ANNUAL REPORT
OF
PROGRAM ACTIVITIES

NATIONAL INSTITUTES OF HEALTH

1963-1964

CLINICAL CENTER
DIVISION OF BIOLOGICS STANDARDS
DIVISION OF RESEARCH FACILITIES AND RESOURCES
DIVISION OF RESEARCH GRANTS
DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

OFFICE OF THE DIRECTOR

CC-01
Serial No.

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Mission

The Clinical Center organization exists to serve patients. Its primary mission is to provide the specialized forms of hospital care needed by both sick patients and normal control volunteers who participate in the clinical research programs of the National Institutes of Health. Another important objective is to provide the most favorable circumstances for medical progress by combining outstanding services and modern facilities with opportunities for young physicians and other professionals to prepare for careers in medical or related research or in academic medicine.

In its administration of the Clinical Center's daily operation, the Office of the Director commands the skills of staff members trained in many specialties. These specialties include: diagnostic x-ray, pharmacy service, laboratory procedures, nursing and dietetic care, social work, medical records, chaplaincy service, rehabilitation, environmental sanitation, and radiation safety.

Accomplishments

During the past 18 months the Clinical Center continued to provide optimum quality care for research patients. This care has been rendered with genuine warmth and personal consideration for the individual. In their dedication to the overall research effort of the National Institutes of Health, members of the hospital staff adhere to the principle that "we cannot afford to overlook the care of today's patients in our zeal to improve the care of tomorrow's patients through research."

Activities of the various Clinical Center departments during the past year and a half are covered in the accompanying specific reports. General program developments, organizational changes, activities under direct supervision of the Office of the Director will be mentioned in the following summary.

Activation of New Surgical Wing

The Clinical Center marked its tenth anniversary in 1963 with the opening of a new surgical wing, painstakingly planned and under construction since 1959, to serve the Cardiac Surgery Branch of the National Heart Institute and the Surgical Neurology Branch of the National Institute of Neurological Diseases and Blindness.

The new addition was dedicated September 5, 1963, at a scientific seminar in which the Surgeon General and many distinguished U. S. and Canadian surgeons participated.

Major innovations of the new wing consist of comprehensive electronic monitoring and recording systems and advanced methods of air hygiene. Utilization of these new facilities since June of 1963 has enabled surgeons to provide the most advanced surgical care for Clinical Center patients, and to collect valuable research data never before obtainable. For example, with the new equipment surgeons can record, recall and instantly compare any combination of patient data during an operation. As experience is gained, computers will be used in conjunction with the monitoring system to develop still more refined techniques for predicting life-threatening crises and thus guiding therapy.

Air-conditioning equipment in the new wing pumps cool, sterile air (less than 1 organism/100 cu. ft.) into the operating rooms through ceiling vents above the operating table and exhausts air through low-level vents. Thus micro-organisms are pulled out near the floor, bypassing the patient.

Another important advantage of the new surgical suite is its circular design which has made it possible to concentrate an aggregation of electronic instruments, and the technicians who operate them, in a centrally located recording room. Consequently, the number of individuals required in the operating room at one time has been reduced from 15 to 7 for cardiac surgery.

The first floor of the new wing houses the Clinical Center Blood Bank and has provided 1,000 sq. ft. of additional space for an expanded and more efficient blood program.

Clinical and Professional Education

An organizational change during the latter part of 1963 placed directly in the Office of the Director responsibility for most of the clinical and professional education activities.

The CC Associate Director, as chief of the Clinical and Professional Education Branch, is responsible for the Residency Programs, the CORD Program, and the Clinical and Research Associate "Matching" Program.

The CC Assistant Director is responsible for the operation of the Television Unit.

The CC Information Officer provides staff assistance for all activities of the Education Committee. This includes editorial service in submitting proceedings of the regular Clinical Staff Conferences and Grand Rounds for publication in professional journals, preparation and distribution of advance publicity materials and minutes of the meetings; handling physical arrangements for meetings and providing staff to register and page the participants during all meetings.

The COSTEP Program, the High School Science Teachers project, and the Orientation programs were transferred to Personnel, OD. Responsibility for the Research Associate Program was also transferred, upon recommendation of the Scientific Advisory Committee.

A detailed account of the newly organized Clinical and Professional Education Branch's activities during the past 18 months is given in the accompanying Summary Annual Report for that branch.

Normal Volunteer Program

As shown in Tables 1 and 2, the total volunteer in-patient days for 1963 increased only 68 days -- from 23,750 to 23,818 -- but there was an increase of 105 in the number of volunteers. This was the result of a deliberate plan to curtail the length of stay of the classic "long-term volunteer." Experience has shown that volunteers who remain too long tend to be of lessening value as research subjects for several reasons. They complete all the studies for which they were admitted and may not qualify for other types of projects. In addition, after a prolonged stay a subtle change comes over the normal, healthy volunteer. Some individuals resent the dependency role the volunteer patient necessarily occupies. They may become indifferent to the rules and regulations of the hospital, thus presenting more of a management problem. There is also a morale factor; the long-term volunteer becomes more sensitive and easily upset by conditions which had been acceptable previously. Thus near the end of his first 90-day period, the average volunteer is looking forward to either his next assignment in one of the religious service organizations or his return to the college campus.

Despite the reduction in the length of stay for individual volunteers, the census in the total number of admissions increased sufficiently to provide replacements required because of the accelerated turn-over and to meet the increased demand for normal volunteers by the various Institute investigators. This successful arrangement was possible because the overall volunteer program has become stabilized after eleven years of operation. Helpful, also, was the addition of two new sponsoring agencies during 1963: Goddard College and the Church of Jesus Christ of Latter Day Saints. The latter sponsor furnishes volunteers for both in-patient and out-patient programs.

During this reporting period, the volunteer out-patient was utilized for medical studies as well as for mental health projects. The number of participating agencies remains the same. However, the Morman Church replaced Maryland University and its contract will provide volunteers for medical studies as well as for those of the Mental Health Institute. It is anticipated that greater use will be made of this section of the normal volunteer program in the future.

Visits made off the reservation by NIMH, NIAMD, and NHI investigators totalled 640 with 6,379 hours. Participating agencies providing volunteers on the contractor's premises included: Brethren Service Commission, Morman Church, American University, and the Montgomery County Mental Health Association.

The participation of Federal prisoner volunteers in the normal volunteer program, begun in 1960, has continued to function exceedingly well. The 1,000th volunteer will be admitted in mid-year 1964 and it is expected that the Clinical Center's present arrangements with the Federal Bureau of Prisons will become permanent. These prisoner volunteers have enabled NIAMD investigators to make substantial progress in their respiratory virus studies. Advances that would have required many years to accomplish with large population groups, have been made within months through the cooperation of these volunteers.

Patient Activity Program

A full-scale patient activity program was achieved in 1962. During the past 18 months the patients' interest in and response to the varied organized recreational activities have indicated the over-all value of the program in maintaining morale favorable to research, to treatment, and to the development of human capacities.

The patients' library is an important part of this program. Use of this facility is shown by the following statistics for the period January 1963 through March 1964: books circulated, 21,666; talking books circulated, 385; interlibrary loans, 186. Members of the library staff provided weekly book cart service without interruption, gave individual assistance to normal control volunteers (particularly the college groups), and arranged for three Mental Health Institute patients to have work experience in the library to prepare them for jobs upon discharge from the hospital. Also, with the help of a volunteer group, a Weekly Bedtime Story Hour for children patients was added to the regular library program. Special library services included providing language records for Spanish and Turkish patients studying English; volunteers were recruited to teach and materials were supplied to help a patient learn Braille, and to assist a group of Spanish-speaking patients to learn English.

Members of the Patient Activity Section staff have established cooperative relationships with many church and civic groups in the community. This arrangement has enabled the staff to provide many elaborate programs for the patients. Gray Service volunteers of the American Red Cross, also, contribute to this patient-centered program by supplementing activities not provided by the NIH staff, such as bedside visiting, shopping, and escort service. Thus a tie with the world outside the hospital is maintained and this is particularly important for long-term research patients who are far from home and family.

Medical Board

The Medical Board for 1963 had a new chairman and one new member. There were a number of changes in appointments to the various committees of the Medical Board.

The Clinical Research Committee was active again this year, principally because of the large number of projects which involved normal volunteers.

The following four amendments were added to the Organization and By-Laws Document:

Amendment No. 21. Revision of Article IV, Section 1, D, Paragraphs No. 2, 17, 20, and 27 regarding change in location of Blood Bank, Orthopedic Surgery, Pediatrics, and Urology.

Amendment No. 22. Additional language defining the functions of the Clinical Pathology Department, Article IV, Section 2, C, Paragraph No. 2; additional sentences defining the functions of the Pathologic Anatomy Department, Article IV, Section 2, C, Paragraph No. 5.

Amendment No. 23. Revision of last sentence defining the functions of the Medical Record Committee of the Medical Board, Article V, Section 6, C, Paragraph No. 2.

Amendment No. 24. Revision of Article IV, Section 1, C, regarding the present alignment of services in the individual Institutes.

Panel of Consultants

During the last 18 months, there were 1,065 visits by medical care consultants to the Clinical Center. Seven medical care consultants have been added to the roster, the total number now being 149.

The system for calling medical care consultants has been satisfactory. Institute staff members responsible for covering a particular specialty are designated as panel chiefs. If a staff member wishes the services of a medical care consultant he notifies the responsible panel chief who then makes arrangements for securing the desired consultant's services. In this manner a consultant can be used by more than one Institute during one visit to the Clinical Center. It is felt that the consultant program has worked very well.

Admission and Occupancy Data

A total of 33,392 in-patients have been admitted since the Clinical Center opened in 1953, eleven years ago. As the clinical research program matures, the number of followup patient visits increases and this figure had reached 213,181 by June 30, 1964. The average daily census for the period January 1, 1963, to June 30, 1964, was 374 and the average length of stay was 38, a slight increase over previous years. Although the average occupancy rate decreased 4 points below the rate for fiscal year 1962, the number of tests and procedures performed in all departments has risen sharply.

The flow of patient referrals from practicing physicians continues to meet the needs of the various Institutes. In keeping with the original plans for the Clinical Center operation, all referrals are formally reviewed and only those meeting the specific requirements of a current study are admitted when there is a bed available.

Widespread sources of patient referrals were pursued during the past 18 months as a matter of continuing policy. However, to facilitate the long-term followup treatments and observations so essential to many of the research projects, recruitment of specific types of patients was limited to nearby areas. Thus 43% of patients admitted during calendar year 1963 and the first quarter of 1964 were from Maryland, Virginia, and the District of Columbia.

After eleven years' operation, it is interesting that the number of pediatric admissions (16 and under) climbed to 1,008, 18% of the total admissions for the past 18 month period. In contrast, 449 patients 16 and under were admitted during fiscal year 1962.

Public Information

The informational and public relations aspects of the Clinical Center's program are handled by the Information Office. The staff manages all inquiries from communications media and aids reporters and editors of newspapers and magazines, science writers, and radio and television personnel in preparation of material for the public. Table 3 provides a list of some of the items about the Clinical Center that appeared in newspapers and periodicals from January 1, 1963, to June 30, 1964. In addition, 54 articles concerning patient care activities were published in the NIH Record, which has a circulation of over 12,000 PHS personnel and other health agencies and research institutions. Table 4 lists radio and TV programs in which Clinical Center staff members participated.

Wide public interest has been shown in the Clinical Center's new surgical wing since it was opened in mid-1963. In preparation for the dedication of this new facility, the CC Information Office issued an advance press release, including extensive press background. This material was the basis for several NIH Record stories on the new wing and its dedication. A 20-page summary report was prepared, and a 2,000-word Surgical Wing brochure was published.

Modern Medicine did an advance feature and provided reprints. One week prior to the dedication Fortune magazine ran a full-page color photograph of surgery in the wing, together with text and a story on electronic monitoring of patients. Washington Post published an advance article with four photographs. Washington Star also published an article. Time and Medical World News writers and photographers were assisted. NBC-TV and CBS-TV were aided in obtaining film footage used on two newscasts. Artwork, slides and other visuals were prepared for staff members participating in the dedication program. A preliminary program was printed, followed by a souvenir program for guests. A tour guide and protocol were prepared and printed. Three extensive bibliographies from NHI, NCI, and NINDB were assembled, edited and printed.

Other aspects of the Information Office activities during the past 18 months included the production of leaflets and brochures to meet specific program needs. Table 5 lists some of these, as well as the titles of clinical staff conference proceedings published during the period covered by this report.

As part of the continuing effort to keep physicians informed of the diagnostic requirements, purposes and methods of those clinical studies for which patients are currently needed, two editions of the brochure, "Current Clinical Studies and Patient Referral Procedures" and 16 announcements of special studies were issued. In addition, two exhibits were produced and shown at local, state, and national medical meetings. Specific information about the exhibit schedule is given in Table 6.

Approximately 150 technical articles and papers by professional staff members were published in specialty journals and presented at medical and scientific meetings during the past 18 months. These manuscripts were reviewed by the Clinical Center Editorial Committee for accuracy and adherence to established policy. Titles of the individual papers are included in accompanying individual department reports.

The Preadmission Unit continued to provide a central service to all Institutes for receiving, recording, analyzing, routing, and following up for study on physicians' referrals of patients. During the past year and a half this Unit processed 7,170 letters and 1,155 telephone inquiries.

There has been a significant increase in the number of physicians coming to NIH to learn more about the clinical research programs. During 1963 and the first half of 1964, the Special Events Section of the Information Office arranged tours and appointments for 813 U. S. physicians and 815 physicians from foreign countries who visited the Clinical Center. In contrast, these visitors in 1962 totalled 297 U. S. physicians and 488 from abroad. Each visiting physician receives selected NIH literature, including "Current Clinical Studies." Many physicians request an opportunity to inspect the patient care facilities prior to referring patients for study. Their usually favorable impressions are a significant factor in maintaining a high level of patient referrals.

The number of scientific and clinical meetings held at NIH increased also. During the past 18 months the Special Events staff coordinated arrangements for 80 clinical and scientific assemblies, attended by almost 20,000 persons. In 1962, these figures were 39 meetings with a combined attendance of about 11,000. It is of interest that clinical topics predominated over basic research subjects at these meetings. Table 7 provides a complete list of the meetings by date, group, and subject.

Table 1

NORMAL VOLUNTEER PATIENT PROGRAM

January 1, 1963 - June 30, 1964

Total Days by Sponsoring Agencies

Agency	Male Days	Female Days	Total Days
Brethren Service Commission	3,619	4,725	8,344
Mennonite Central Committee	1,089	827	1,916
Antioch College	1,611	1,112	2,723
Goddard College	820	443	1,263
Johnstown City-County Clinic	2,853	411	3,264
Morman Church	0	2	2
Federal Bureau of Prisons	12,299	0	12,299
Total:	22,291	7,520	29,811

Number of Volunteers and Days by Institutes

	VOLUNTEERS			DAYS		
Institute	Male	Female	Total	Male	Female	Total
NIAID	375	2	377	12,919	90	13,009
NIMH	91	76	167	3,377	2,337	5,714
NIAMD	61	46	107	1,682	1,101	2,783
NCI	19	9	28	1,123	570	1,693
NHI	34	49	83	2,690	3,309	5,999
NINDB	5	3	8	401	212	613
NIDR	0	0	0	0	0	0
	585	185	770	22,192	7,619	29,811

Number of Volunteers per Sponsoring Agency

Agency	Male	Female	Total
Brethren Service Commission	129	139	268
Mennonite Central Committee	16	9	25
Antioch College	21	14	35
Goddard College	14	10	24
Johnstown City-County Clinic	38	11	49
Morman Church	0	2	2
Federal Bureau of Prisons	367	0	367
	585	185	770

Table 1 - (Continued)

Estimated Remaining Volunteers on June 30, 1964

Institute	Volunteers	Volunteer Days
NIAID	29	821
NIMH	6	168
NIAMD	13	294
NCI	6	130
NHI	18	396
NINDB	2	44
NIDR	0	0
Total:	74	1,853

TOTALS FOR 18 MONTHS

May 28 through June 30, 1964 estimated

Institute	Discharged Volunteers	Remaining Volunteers (Estimated)	Total Volunteers	Total Patient Days
NIAID	377	29	406	13,830
NIMH	167	6	173	5,882
NIAMD	107	13	120	3,077
NCI	28	6	34	1,823
NHI	83	18	101	6,395
NINDB	8	2	10	657
NIDR	0	0	0	0
	770	74	844	31,664

Table 2

NORMAL VOLUNTEER PATIENT PROGRAM OUT-PATIENT REPORT

January 1, 1963 to June 30, 1964

Per Clinic Visit
Participating Agencies

Agency	Total Visits	Total Hours
Brethren Service Commission	232	
American University	320	733
Montgomery Junior College	602	1,040½
Montgomery County Mental Health Association	732	1,603
Retired Civil Employees	128	319
Morman Church	77	190
	2,091	3,885½

Participating Institutes

Institute	Visits Per Institute	Hours Per Institute
NIMH	2,011	3,715½
NIAMD	38	66
NHI	42	104
	2,091	3,885½

Away from Reservation
Participating Agencies

Agency	Total Visits	Total Hours
Brethren Service Commission	77	
Morman Church	563	818
American University		346
Montgomery County Mental Health Association		5,215
	640	6,379

Participating Institutes

Institute	Visits Per Institute	Hours Per Institute
NIMH	77	5,561
NIAMD	555	810
NHI	8	8
	640	6,379

NOTE: The above figures only reflect the months of January 1, 1963 to April 30, 1964.

Table 3

SOME ITEMS THAT APPEARED IN NEWSPAPERS AND MAGAZINES

January 1, 1963 - June 30, 1964

Blood Donors at NIH Get Red Cells Back, Evening Star, Aug. 2, 1963.

NIH Revolving Altar Serves Three Faiths, Evening Star, Aug. 3, 1963.

Technology and Surgeons Combine Their Talents, Wash. Post, Aug. 29, 1963.

Surgery-in-the-round at NIH, Mod. Med. 31: 32-38, Sept. 2, 1963.

Surgical Palace: NIH Wing to Feature Heart, Brain Surgery, Evening Star, Sept. 4, 1963.

$2 Million NIH Surgical Wing to Open, The Suburban Record, Sept. 5, 1963.

New $2 Million Surgical Wing at NIH is Dedicated, The Tribune, Sept. 6, 1963.

Surgery: Operating Rooms-in-the-Round, Time, Sept. 13, 1963.

The Transistorized M.D., Fortune, Sept. 1963.

Announcement of the appointment of the Rev. LeRoy G. Kerney as supervisory chaplain in the CC appeared in the Wash. Post, Sept. 18 and the Evening Star, Sept. 21, 1963.

Advanced Surgery at NIH, Science News Letter, Sept. 28, 1963.

Surgery in the Round, Med. World News, Oct. 11, 1963.

Machine Gives Out Instant Data, Life Mag. Dec. 6, 1963.

For Jail Guinea Pigs, It Pays to Get Sick, Wash. Post, Feb. 9, 1964.

What Goes on Here column of Wash. Daily News, Feb. 29, 1964, item on donation of 62 pints of rare A-B Positive (with C-factor) blood for CC heart surgery patient.

Surgery Uses 62 Donations of Rare Blood, Wash. Post, Feb. 29, 1964.

U.S.A. New Surgical Wing, CC NIH of Bethesda, Int. Hosp. Fed. News Bull. No. 71: 4-8, Mar. 1964.

Medical Monitoring System Holds Lesson for Industry, Graphic (pub. by Esterline Angus Instrument Co., Inc.), Bull. No. 464, 1964.

Table 3
(Continued)

Electronic Monitoring of the Critically Ill, Milit. Med. 129: 343-348 Apr. 1964.

News from NIH, Dent. Abst. 9: 209-210, Apr. 1964.

Electronic Monitoring System for Surgery at NIH, Anal. Chem. 36: 31A-39A, May 1964.

NIH: Opportunities in Training, House Phys. Rep. 4: 1-3, May-June, 1964.

Sistema Circular: De Cardio Cirugia y Neurocirugia, El Hosp. 20: 21-24, June 1964.

Chaplain Honored at Rites, Bethesda-Chevy Chase Tribune, June 12, 1964.

Chaplain Honored (Rev. LeRoy G. Kerney), Sentinel, Montg. County, Md. June 18, 1964.

Rev. Kerney Installed As Chaplain at NIH, The Suburban Record, June 26, 1964.

Patients Given "Pay" for Being Sick, Evening Star, June 26, 1964.

TABLE 4

RADIO AND TV PROGRAMS CONCERNING CLINICAL CENTER ACTIVITIES OR STAFF MEMBERS

January 1, 1963 - June 30, 1964

1963

Mar. 6	WRC's radio news feature "Capital Bylines" included interview with Dr. Clifton K. Himmelsbach, CC Associate Director, and two normal volunteer patients.
May 21	Voice of America carried an interview by Terry Baker with Dr. Clifton K. Himmelsbach, CC Associate Director, and two normal volunteer patients.
June 7	WJAR-TV of Providence, R. I., taped an interview with Dr. Jack Masur, CC Director.
Aug. 1	CBS-Radio feature "Women of Washington" carried an interview with Dr. Jane Wilcox, CC Special Assistant for Nursing Research.
Sept. 5	NBC-TV and CBS-TV newscasts featured the Clinical Center's new surgical wing.
	WTOP and WMAL Radio carried news stories about the dedication of the Clinical Center's new surgical wing.
Sept. 23	Radio Free Europe taped Martin Bush's interview with Dr. Robert M. Farrier, CC Assistant Director, concerning the electronic monitoring system in the Clinical Center's new surgical wing.
Sept. 26	NBC-TV feature "Inga's Angle" included an interview with Dr. Jane Wilcox, CC Special Assistant For Nursing Research.

1964

May 13	CBS-TV NEWS FEATURES included a 5-minute report by Neal Strawser on "Volunteer Program of the National Institutes of Health."

Table 5

PRINTED MATERIAL

January 1, 1963 - June 30, 1964

PUBLICATIONS

Current Clinical Studies and Patient Referral Procedures (Rev. Mar. 1963)

Nursing at the Clinical Center, PHS Pub. 468 (Rev. 1963 and 1964)

Patient Admission Procedures, PHS Pub. 500 (Rev. 1963)

Clinical Center Diet Manual, PHS Pub. 989 (First ed. 1963)

Surgical Wing of the Clinical Center (First ed. 1963)

Clinical Center of the National Institutes of Health, PHS Pub. 316 (Rev. 1963)

Handbook for Patients at the Clinical Center (Rev. 1963)

Handbook for Gray Service Volunteers (Rev. 1963)

The Normal Volunteer Program of the NIH, PHS Pub. 866 (Rev. 1963)

Current Clinical Studies and Patient Referral Procedures (Rev. Mar. 1964)

Opportunities for Clinical and Professional Education at NIH, PHS Pub. 1127 (Mar. 1964)

You and Your Job (First handbook to be prepared for employees of CC's Dept. of Environmental Sanitation Control)

Handbook for the Normal Volunteer Patient Program (Apr. 1964)

Handbook for Staff Physicians (Rev. July 1, 1964)

Blood Insurance Policy (1963)

Blood Facts (1963)

How Your Blood Donations Are Used (1963)

Current Clinical Research at NIH (1964) -- To accompany the CC exhibit

Table 5
(Continued)

POSTERS

Three for Blood Bank

Federal Employee Health Insurance Program

Opportunities for Clinical and Professional Education

COMBINED CLINICAL STAFF CONFERENCES

"Aortic stenosis: Physiological, pathological, and clinical concepts." Ann. Intern. Med. 58: 494-522, Mar. 1963.

"Neoplastic plasma cell." Ann. Intern. Med. 58: 1017-1036, June 1963.

"Symposium on Malaria." Part 1, JAMA. 184: 872-877, June 15, 1963. Part 2, JAMA. 184: 943-947, June 22, 1963. Part 3, JAMA. 184: 1018-1023, June 29, 1963.

"Current studies on the effect of antimetabolites in nephrosis, other non-neoplastic diseases, and experimental animals." Ann. Intern. Med. 59: 388-407, Sept. 1963.

"Folic acid antagonists: Effects on the cell and the patient." Ann. Intern. Med. 59: 931-956, Dec. 1963.

"A mechanism of cell destruction in individuals sensitized to foreign antigens and its implications in auto-immunity." Ann. Intern. Med. 60: 506-521, Mar. 1964.

"The surgical management of mitral valve disease: A symposium on diagnostic methods, operative techniques, and results." Ann. Intern. Med. 60: 1073-1100, June 1964.

Table 6

SHOWINGS OF CC EXHIBIT: "CURRENT CLINICAL RESEARCH AT NIH"
January 1, 1963 - June 30, 1964

1963	Meeting	Location
Jan. 16-18	Northern Virginia Cancer Nursing Institute	Clinical Center, NIH
Feb. 18-20	Assoc. of Operating Room Nurses	Washington, D. C.
Mar. 18-21	American Industrial Health Conference	Washington, D. C.
Apr. 1-5	American College of Physicians	Denver, Colo.
May 1-3	Med. & Chir. Faculty (Md.)	Baltimore, Md.
May 9-12	Virginia Academy of General Practice	Richmond, Va.
June 16-20	American Medical Assoc. Annual	Atlantic City, N.J.
Aug. 26-29	American Hospital Assoc.	New York City Coliseum
Oct. 9-12	Pennsylvania Med. Society	Pittsburgh, Pa.
Oct. 14-16	Md., D.C., & Del. Hospital Assoc.	Washington, D.C.
1964 (New exhibit; same title)		
Apr. 6-10	Amer. Coll. of Physicians	Atlantic City, N. J.
Apr. 13-16	Amer. Acad. of Gen. Prac. Scientific Assembly	Atlantic City, N. J.
May 2-6	Med. Soc. State of N.C.	Greensboro, N.C.
May 18-20	Med. Soc. of N. J.	Atlantic City, N. J.
Exhibit: "A Look at the Development of a New Drug"		
1963		
Mar. 18-21	American Industrial Health Conference	Washington, D.C.

Table 7

MEETINGS HELD AT THE CLINICAL CENTER

January 1, 1963 - June 30, 1964

Northern Virginia Cancer Nursing Institute, January 17.

Medical Research Fellowship Seminar for Montgomery County High School Students, January 19.

Combined Clinical Staff Conference - NCI, January 24.

Medical Research Fellowship Seminar for Montgomery County High School Students, January 26.

Medical Research Fellowship Seminar for Montgomery County High School Students, February 2.

Peripatetic Club Meeting, February 8.

Medical Research Fellowship Seminar for Montgomery County High School Students, February 9.

Combined Clinical Staff Conference - NIMH, February 14.

NIH Lecture - Dr. De Witt Stetten, Jr., February 27.

Lecture - Dr. Ingmar Wickbom, March 4.

D.C. Chapter of the American Physical Therapy Association, March 5.

Commissioned Corps Indoctrination, March 7.

Meeting of the American Academy of Child Psychiatry, March 15.

NIMH Seminar - "The Need for Pharmacology of Chronic Treatment" by Professor Eleanor Zaimis, March 18.

Combined Clinical Staff Conference, March 21.

Eastern Gut Club, March 23.

NIH Orientation Program, March 26.

American Epidemiological Society Meeting, April 5-6.

First American Meeting of the Royal Microscopical Society, April 7-9.

The R. E. Dyer Lecture - Dr. Salvador E. Luria, April 25.

Fifth Annual Meeting of the Council on Medical Television, May 6-7.

Combined Clinical Staff Conference, May 9.

Twelfth Annual Awards Ceremony, May 15.

Annual Cardiac Symposium - Co-sponsored by the Montgomery County Tuberculosis and Heart Association and the NHI, May 16.

Scientific Seminar to observe the 15th Anniversary of the NIDR, June 14.

COSTEP Orientation Program, June 25.

Special Orientation program for new Commissioned Officers who EOD on 7/1/63, July 8.

NIH Orientation Program for new employees, July 16.

Commissioned Officers' Question and Answer Period, August 7.

Dedication of the new surgical wing of the Clinical Center, September 5.

NIH Lecture - Dr. Alfred Blalock, September 5.

Nursing Symposium: The Child with Congenital Heart Disease, September 12.

Lecture: "The History of Psychiatry in England, 16th to 19th Centuries. A Bibliographical Tour." Dr. Richard Hunter, Department of Physiological Medicine, National Hospital for Nervous Diseases, London, England, September 19.

Meeting of the District of Columbia Chapter of the American Physical Therapy Association, October 1.

Annual Jules Freund Memorial Lecture, October 7.

Symposium on Recent Developments in Research Methods and Instrumentation held in conjunction with the NIH 13th Annual Research Equipment Exhibit, October 7-10.

First NIH International Lecture, October 31.

NIAID Assembly of Scientists, November 8.

Lecture Sponsored by the Foundation for Advanced Education in the Sciences, November 20.

Annual Frieda Fromm-Reichmann Memorial Lecture, November 22.

Maryland State Dental Association, December 11.

Combined Clinical Staff Conference, January 9.

Medical Grand Rounds, January 16.

NIH Federal Credit Union, January 16.

Medical Research Seminar for High School Students, January 25.

Combined Clinical Staff Conference, January 30.

Committee on Drug Addiction & Narcotics, NAS-NRC, February 4.

A NIH Lecture - Dr. Robert K. Merton, February 5.

Combined Clinical Staff Conference, February 13.

Montgomery County T.B. & Heart Association, February 18.

A NIH Lecture - Dr. Jacques Monod, February 19.

Medical Grand Rounds, February 20.

Foundation for Advanced Education in the Sciences, Inc., February 26.

Keymen for Federal Service Crusade, February 28.

D. C. Chapter of the American Physical Therapy Association, March 3.

Meeting of Commissioned Officers leaving NIH, March 5.

Tuesday-Seminar - Laboratory of Psychology, March 10.

Combined Clinical Staff Conference, NIMH, March 12.

Medical Grand Rounds, NHI, March 19.

Meeting of the local branch of the American Society for Microbiology, March 24.

Foundation for Advanced Education in the Sciences, March 25.

Combined Clinical Staff Conference, March 26.

Annual Meeting of the American Academy of Oral Pathology, April 2-4.

American Association of Endodontists, April 16.

DBS-Lecture, April 21.

Middle Atlantic Society of Surgeons, April 23.

New York University Rehabilitation Department, April 25.

Columbia University Hospital Administrators, April 28.

R. E. Dyer Lecture - Dr. Harry Rubin, April 29.

American Association for the History of Medicine, April 30.

American Association for the History of Medicine, May 1.

American Society of Microbiology, May 6.

Foundation for Advanced Education in the Sciences, May 8.

Annual Awards Ceremony, May 19.

Fifth Annual Cardiac Symposium, May 21.

Third Annual Conference of the Mental Health Career Development Program, May 27-28.

Combined Clinical Staff Conference, NHI, May 28.

Combined Clinical Staff Conference, June 11.

Computer Demonstration, June 15.

Health Education Program, June 17.

Distinguished Foreign Visitors

Mr. Nikolai F. Izmerov, Deputy Chief, Department of Foreign Relations, Ministry of Health, Moscow, U.S.S.R.

Mr. Denis N. Kalyuzhny, Director of Department of Communal Hygiene, Kiev Medical Institute, Kiev, U.S.S.R.

Mr. Marra K. Nedogibchenko, State Sanitary Inspector, Ministry of Health, Moscow, U.S.S.R.

Mr. Otar P. Shalamberidze, Deputy Director, Tbilisi Scientific Research Sanitary and Hygiene Institute, Tbilisi, U.S.S.R.

Dr. Yuri M. Vasiliev, Scientific Vice Director, Institute of Experimental and Clinical Oncology, Moscow, U.S.S.R.

Former King Leopold and Princess Liliane, Belgium.

Ambassador Louis Scheyven, Embassy of Belgium, Washington, D.C.

Dr. Louis Groven, Scientific Attache, Embassy of Belgium, Washington, D.C.

Dr. Vempaty Rao, Deputy Director, National Malaria Eradication Program, Ministry of Health, India.

Dr. Gyaneshwar Sharma, Assistant Director, National Malaria Eradication Program, Ministry of Health, India.

Dr. Kunarapura Krishnan, Assistant Director, National Malaria Eradication Program, Ministry of Health, India.

Dr. Ram Rakha Arora, Assistant Director, National Malaria Eradication Program, Ministry of Health, India.

Dr. Subramania Ramani, Chief Entomologist, National Malaria Eradication Program, Ministry of Health, India.

Dr. Richard Wilhelm Martin, Medical Director of Hessen - Sanitorium, Bad Nauheim, West Germany.

Dr. Laerte Manhaes de Andrade, Head of the Section of Bioclimatology, Division of Hygiene, Institute Oswaldo Cruz, Rio de Janeiro, Brazil.

Professor Nygaard Ostby, Department of Odontology, University of Oslo, Oslo, Sweden.

Professor P. K. Anokhin, Member of the Academy of Sciences, USSR, Professor of Physiology at the Moscow University, U.S.S.R.

Mr. Gordon Hughes, Chief, Hospital Design Division, Canadian Department of National Health and Welfare, Canada.

Professor Eleanor Zaimis, Department Chairman of Pharmacology, Royal Free Hospital School of Medicine, London, England.

Dr. Dora Siew Kew Tan, Virus Research Officer, Institute for Medical Research, Kuala Lumpur, Malaya.

Dr. Milota Gresikova, Institute of Virology, Bratislava, Czechoslovakia.

Dr. Alfredo Afanador, Director of Institute of Health, Administration of Public Health, Colombia.

Professor Paul Ponthus, Directeur, Institut de Radiologie et de Lutte Contre le Cancer, Beyrouth, Lebanon.

Dr. M. E. A. Kharadly, Executive Director, Anti-Cancer Association and Patients' Care, Alexandria, Egypt, UAR.

Dr. and Mrs. Carmen Annes Dias Prudente, Fundacao Ofensive Contra O Cancer, Rio de Janeiro, Brazil.

Dr. D. J. Jussawalla, Honorary Secretary, Indian Cancer Society, Bombay, India.

Mr. Niilo Voipio, Secretary General, The Cancer Society of Finland, Helsinki, Finland.

Dr. J. F. Delafresnaye, Director, Geneva Office, UICC, Geneva, Switzerland.

Dr. Albert Mondet, Secretary of Public Health, Buenos Aires, Argentina.

Dr. Florentino L. Alen, Director General of Public Health, Buenos Aires, Argentina.

Dr. Boon Suvarnasa, Deputy Director General of Health, Thailand.

Dr. Guillermo Jauregui, Minister of Health, Bolivia.

Dr. Tiburcio Padilla, Minister of Health, Argentina.

Dr. A. A. Pokrovsky, Corresponding Member of the USSR Academy of Sciences and Director of the Academy's Nutrition Institute, U.S.S.R.

Dr. Ye. S. Zhdanovich, Candidate of Medical Sciences and Deputy Director of Science for the All-Union Vitamins Research Institute of Moscow, U.S.S.R.

Dr. M. I. Smirnov, Candidate of Biological Sciences and Director of the Moscow Vitaminology Research Institute, U.S.S.R.

Dr. Ye. F. Shamray, Professor, Chairman of the Biochemistry Department, Kiev Institute, U.S.S.R.

Dr. M. G. Shevchenko, Chief Inspector for Nutritional Hygiene of the State Health Inspection, USSR Ministry of Health, U.S.S.R.

Professor Lukas, Deputy Minister of Health, Czechoslavakia.

Dr. Boris Semenov, Neuro-Virus Laboratory, Moscow Scientific Research Institute for Virus Preparations, Moscow, U.S.S.R.

Dr. Toh Chin Chye, Deputy Prime Minister of the State of Singapore and Chairman of the Board of Directors, Singapore Polytechnic Institute, Malaya.

Dr. E. B. S. Lumu, Minister of Health, Uganda.

Lord Taylor, Assistant Editor of Lancet, London, England.

Hon. Louis Scheyven, Belgian Ambassador.

Mr. Viktor Mikhailovich Ilyukhin, Soviet Hospital Management Delegation, U.S.S.R.

Dr. Palina Ivanovna Kovalenko, Soviet Hospital Management Delegation, U.S.S.R.

Mrs. Mariya Prokofevna Perepelitsina, Soviet Hospital Management Delegation, U.S.S.R.

Mr. Aleksei Georgievich Safonov, Soviet Hospital Management Delegation, U.S.S.R.

Dr. Yuri Efimovich Danilov, Soviet Hospital Management Delegation, U.S.S.R.

Dr. Aleksandr Vladimirovich Sergeev, Soviet Hospital Management Delegation, U.S.S.R.

Dr. A. K. Mufarrij, President, Lebanese Medical Association, President, Lebanese Order of Physicians, Associate Professor of Anatomy, American University of Beirut Medical School, Beirut, Lebanon.

Dr. Juna Antonio Montalvan-Cornejo, Director, National Institute of Hygiene, Guayaquil, Ecuador.

Miss Athena Saltafera, Stepdaughter of the Greek Ambassador.

Mrs. Marcos C. Economides, Wife of First Secretary, Embassy of Greece.

Dr. Govinda Reddy, Executive Director of the Indian Association for the Advancement of Medical Education, Madras, India.

Dr. Mohammed Ibrahim, Principal and Professor of Medicine, Mitford College, Dacca, Pakistan.

Dr. Simon Btesh, Director of Research and Coordination, World Health Organization, Geneva, Switzerland.

Dr. N. Akim, Chief Medical Officer, Ministry of Health, Salam, Tanganyika.

Capt. and Mrs. Kiyohide Seki, Naval Attache, Embassy of Japan.

Mr. C. A. Nettle, Assistant Commissioner, Australian Repatriation Commission, Australia.

Mr. D. F. Tierney, Australian Repatriation Commission, Australia.

Professor Wlodzimierz Kurylowicz, Chairman, Polish Coordinating Committee, PHS--P.L. 480 Research Agreement, Poland.

Dr. Igor Tereshchenko, Head, Laboratory of Pathological Physiology, State Scientific Research, Oncological Institute i.m. Gersten, USSR Ministry of Health Protection, Moscow, U.S.S.R.

Humphrey Malmo Samuel Boardman, Chief Medical Officer, Ministry of Health, Sierra Leone.

Joseph Theophilus Oluwole Vincent, Dental Surgeon Special Grade, Ministry of Health, Sierra Leone.

Olive Vivat Kulu Johnson, Principal Matron, Ministry of Health, Sierra Leone.

Dr. H. Selle, Commissioner of Hospitals, Sydney, Australia.

Dr. A. G. Fedotenkov, Head, Laboratory of Tissue Conservation, Central Institute of Hematology and Blood Transfusions, Moscow, U.S.S.R.

Dr. Constantinos Tountas, Professor of Surgery and Director of the First Surgical Clinic of AHEPH Hospital, Thessaloniki University, Thessaloniki, Greece.

The Governor and Mrs. Guerrera, Guam.

Manuel U. Lujan, Vice Speaker, Guam Legislature, Agana, Guam.

Dr. Komol Pengsritong, Under Secretary of State for Food and Drug Administration, Government of Thailand.

Dr. Marcelino Bienvenido Velez Santana, President, Dominican Medical Association, Professor of Medicine, Faculty of Medicine, University of Santo Domingo, Head, Bacteriological Services, Salvador Gautier Hospital, Dominican Republic.

Senora Marie Salazar de Duran (M.D.), Chile.

Senora Guitierrez-Olivos, Wife of the Ambassador, Chile.

Dr. Bayardo Burbano, Dentist in Private Practice, Member, National Executive Committee of the Social Democratic Party of Ecuador, Tulcan, Ecuador.

Dr. Manohar Singh Chadha, Director General of Health Services, Ministry of Health, Government of India, New Delhi, India.

Gerrit Siwabessey, M.D., Director General, Institute of Atomic Energy, Director, Institute of Radiology, Djakarta, Indonesia.

Mme. B. K. Nehru, Ambassador from India.

Mme. Petre Balaceanu, Wife of Ambassador from Rumania.

Professor Jean-Pierre Gillet, Administrator, Free University of Brussels, Belgium.

His Excellency Ato Yohannes Tsege, Vice Minister of Health of Ethiopia, Addis Ababa, Ethiopia.

Dr. G. A. Alekseyev, Soviet Hematology Delegation, U.S.S.R.

Dr. M. P. Bogoyavlenskaya, Soviet Hematology Delegation, U.S.S.R.

Dr. A. N. Filatov, Soviet Hematology Delegation, U.S.S.R.

Dr. N. S. Kislyak, Soviet Hematology Delegation, U.S.S.R.

Dr. I. I. Zaretskiy, Soviet Hematology Delegation, U.S.S.R.

Dr. A. G. Fedotenkov, Chief, Laboratory of Tissue Preservation, Central Institute of Blood Transfusion, Moscow, U.S.S.R.

Dr. Valentin Zolotorevsky, Senior Scientist, Vishnevsky Surgery Institute, USSR Academy of Medical Sciences, Moscow, U.S.S.R.

Prof. Pavel N. Napalkov, Head of the Chair of Surgery, Leningrad Sanitary-Hygienic Medical Institute, Leningrad, U.S.S.R.

Mr. Aleksandr Izvekov, Third Secretary, Embassy of the U.S.S.R.

Five member Delegation from the Polish National Academy of Sciences.

Professor Chakiri Balakirshnan, Department of Plastic Surgery, Nagpur, India.

Professor Boris Alekseyevich Korolev, Chief, Department of Hospital Surgery, Gorkiy Medical Institute, USSR Academy of Medical Sciences, U.S.S.R.

Dr. Ol'ga Danilova Kolyutskaya, Chief of the Laboratory of Anesthesiology of the Scientific Research Institute of Experimental Surgery, R.S.F.S.R. Ministry of Health.

Dr. Nikolay Vasil'yevich Menyaylov, Chief, Department of Anesthesiology, Central Institute of Traumatology and Orthopedics, U.S.S.R. Ministry of Health.

Dr. Gennadiy Alekseyevich Ryabov, Chief, Laboratory of Anesthesiology, Institute of Thoracic Surgery, U.S.S.R. Academy of Medical Sciences.

Dr. Anatoliy Ivanovich Treshchinskiy, Department of Thoracic Surgery and Anesthesiology, Kiev Institute for the Advanced Training of Physicians, U.S.S.R.

Dr. Dmitriy Aleksandrovich Kharkevich, Professor, Department of Pharmacology, First Moscow Medical Institute, U.S.S.R.

Professor N. M. Emanuel, Laboratory Director, Institute of Chemical Physics, Academy of Sciences, Moscow, U.S.S.R.

Seventeen Delegates to the Association of Military Surgeons

Professor Michio Okamoto, Head, Department of Kyoto University Medical School, Kyoto, Japan.

Professor and Mrs. N. N. Blokhin, President, USSR Academy of Medical Sciences, Moscow, U.S.S.R.

Dr. Boris A. Lapin, Scientific Director, Sukhumi Institute of Experimental Pathology and Therapeutics, Academy of Medical Sciences, Sukhumi, U.S.S.R.

Dr. Miranda Gutierrez, Dean, San Jose Medical School, Costa Rica.

Professor Joon Lew, Department of Microbiology, Yonsei University College of Medicine, Seoul, Korea.

Col. Anil Krishnan Barat, Professor of Surgery, Indian American Forces Medical College, Poona, India.

Col. Biradavolu Durga Prasad Rau, Professor of Pathology, Indian American Forces Medical College, Poona, India.

Professor G. R. K. Hari Rao, Department of Anatomy, Medical College, Andhra Pradesh, India.

Mrs. A. Arturo Rivera, Wife of Minister Counselor, Embassy of Guatemala

Mrs. H. Olivero, Guatemala.

Sir Arthur Aimes, Vice Chancellor and Dean, School of Dentistry, University of Melbourne, Melbourne, Australia.

Professor Raul Calvi, Director, School of Rehabilitation, Buenos Aires, Argentina.

Dr. Vladimir S. Shapot, Head, Laboratory of Biochemistry, Institute of Experimental and Clinical Oncology, Moscow, U.S.S.R.

Dr. Igor G. Balandin, Institute of Biological and Medical Chemistry, Academy of Medical Sciences, Moscow, U.S.S.R.

Dr. Sergei S. Debov, Professor of the Chair of Biochemistry, 1st Moscow Medical Institute, Moscow, U.S.S.R.

Professor J. Francis, Veterinary School, University of Queensland, St. Lucia, Australia.

Dr. George D. Katsafados, President, Hellenic Cancer Society, Athens, Greece.

Dr. Anatoly NikolaevichKlimov, Chief, Laboratory of Biochemistry of Lipids, Kirov Military Medical Academy, Leningrad, U.S.S.R.

Professor Ivo Padovan, Medical Faculty and Vice Director of Institute of Scientific Research, "Dr. Mladen Stojanovic" Hospital, Zagreb, Yugoslavia.

Madame Aage Hessellund-Jensen, Wife of Danish Ambassador to the U.N.

Mrs. Roy Petchey, Wife of Air Attache, Andover, England.

Dr. Krishnaswami Rao, Representative of the Central Ministry of Health, India.

Dr. Muktha Sen, Director, All India Institute of Hygiene and Public Health, Calcutta, India.

Col. Chetterjee, Director of Health, West Bengal State, India.

Dr. Marakar, Director of Health, Madras State, India.

Dr. Gopolaraj Chetty, Director of Health, Mysore State, India.

Dr. Patel, Director of Health, Punjab State, India.

Dr. Bhathia, Director of Health, Gujerat State, India.

Dr. Leo Kaprio, Director, Public Health Services, World Health Organization, Geneva, Switzerland.

Professor Lucio Severi, Director, Institute of Anatomy and Pathological Histology, Perugia, Italy.

Dr. Jacques Monod, Pasteur Institute, Paris, France.

Dr. Alexander V. Zaporozhets, Director, Research Institute on the Upbringing of the Preschool Child, Moscow, U.S.S.R.

Professor A. A. Smorodintsev, Head, Division of Virology, Institute of Experimental Medicine, Leningrad, U.S.S.R.

Professor and Mrs. Jose L. Badano, Department of Surgery, Montevideo, Uruguay.

Dr. Kenneth Lloyd Williams, Senior Surgical Registrar, Middlesex Hospital, London W.1, England.

Dr. Catherine Dennis, Ministry of Health, Alexander Fleming House, Elephant and Castle, London, S.E. 1, England.

Dr. Arne R. Krogsgaard, Senior Registrar, Frederiksberg Hospital, Copenhagen, Denmark.

Professor L. M. Shabad, Head, Laboratory of Experimental Oncology, Institute of Oncology, Academy of Medical Sciences, Leningrad, U.S.S.R.

Dr. Fikret Gokay, Professor of Preventive Medicine, Medical School, Izmir, Turkey.

Dr. I. O. Joffe, Hebrew University, Tel Aviv, Israel.

Dr. Roelof Johannes Krusinga, Director, Scientific Research and Planning, Ministry of Social Affairs and Health, The Netherlands.

Dr. Jan Svoboda, Czechoslovak Academy of Sciences, Prague, Czechoslovakia.

Dr. Jean Komouma Terrasson, Medical Inspector of School Health, Department of School Hygiene, Abidjan, Ivory Coast.

Dr. Julien Sylla-Roux, Director of Health of the Central and North Departments of Ivory Coast, Department of Health, Bouake, Ivory Coast.

Dr. Ignace Dyomand Diplo, Director of Health of the South, East and West Departments of Ivory Coast, Ministry of Health, Abidjan, Ivory Coast.

Dr. Theodore Bitty, Director of Public Health Statistics, Ministry of Health, Abidjan, Ivory Coast.

Professor E. Osetowska, Zaklan Neuropathologju PAN, Nenchi Institute, ul Pastura 3, Warsaw, Poland.

Dr. Alicja Stefanicka-Wiechowa, Klinkda Neurochirurgiczna, Akademja Medyczna, ul. Botaniczna 3, Krakow, Poland.

Dr. L. A. Zilber, Head, Department of Immunology & Oncology, Gamaleya Institute, Moscow, U.S.S.R.

Professor Ouay Ketusinh, Department of Physiology, Siriraj Medical School, University of Medical Sciences, Bangkok, Thailand.

Major General Robert Stephen, Consultant in Surgery with War Office in London, England.

Professor Fred G. Kergin, Surgeon, University of Toronto, Toronto, Canada.

Dr. Zdzislow Suwala, Director, Middle Medical Schools, Ministry of Health & Social Welfare, Warsaw, Poland.

Dr. Nadezhda Puchkovskaya, Professor of Medicine and Director of the Research Institute for Eye Diseases, Kiev, Russia.

Professor N. Christeas, Department of Surgery, Athens University, Athens, Greece.

Major General Pornpiskanok, Bangkok, Thailand.

Mr. Konthi Suphamongkhon & Wife, Secretary General, SEATO.

Mr. Curnow, Deputy Information Officer, SEATO.

Dr. Munir Chaura, Deputy Director, School of Medicine, Damascus University, University of Paris, Paris, France.

Dr. Jolanta Patrocka, Sttetin, Poland.

Professor W. Peter Cockshott, University College Hospital, Ibadan, Nigeria.

Professor Satya Nand, Department of Surgery, Medical College, Pondicherry, India.

Dr. Francisco Sison, Manila, Philippines.

Dr. Cristino L. Lazatin, Scientific Attache, Philippine Embassy.

Dr. Antiano Ortiz, Professor of Pediatrics, University of Puerto Rico.

Dr. Ebo Atta, Associate Professor of Endermic Medicine, Cairo University, Cairo, Egypt.

Dr. Francisco Piedrahita, Director of Nutrition, Ministry of Health, Bogata, Colombia.

Dr. and Mrs. Victor Soreano, Professor of Medicine, Calle Buenos Aires 363, Montevideo, Uruguay.

Dr. Puagtong Tantiwongse, Ministry of Health, Thailand.

His Excellency Dr. Abdul Majid, Ambassador of Afghanistan.

Dr. Ishwar Dass Bajaj, Warden, Maulana Azad, College Hostel, New Delhi, India.

Dr. Sharaschandra P. Koranne, Department of Anatomy, Grant Medical College, Bombay, India.

Dr. Sombun Phone-Aksara, Deputy Minister of Health, Thailand.

Dr. Nafis Sadek, Health Section, National Planning Commission, Pakistan.

Dr. LenFranko, Assistant Dean, University of San Marcos, Lima, Peru.

Dr. G. Eyzrauirre, Lima, Peru.

Dr. and Mrs. Arao Imamura, Director of the Center for Adult Diseases, Osaka, Japan.

January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

CLINICAL & PROFESSIONAL EDUCATION BRANCH

CC-02
Serial No.

General:

During the latter part of 1963 following the transfer of Dr. Murray C. Brown to PHS-DOH and of Mr. Joseph Staton to Personnel, OD, a major reorganization of this branch resulted in the following changes:

1. The COSTEP program, the High School Science Teachers project, and the Orientation programs were transferred to Personnel, OD.

2. The Television Unit was transferred to the Assistant Director, CC.

3. Dr. Leonard Laster was designated Chairman of the Education Committee with the Information Office, CC, assisting him with staff work involved in its activities.

4. Upon the recommendation of the Scientific Advisory Committee, Dr. Christian Anfinsen was appointed to head the Research Associate Program effective July 1963.

The following activities remain in the Clinical & Professional Education Branch, with the Associate Director, CC, serving as its Chief:

A. The Residency Programs
B. The CORD Program
C. The Clinical & Research Associate "Matching" Program

A. <u>The Residency Programs</u>

The Clinical Center professional departments providing complete training in specialty fields (including research training in components that are not available elsewhere) are:

Service	Approved	Residents Currently in Training
Anatomical Pathology [1]	3 years	7
Clinical Pathology [1]	3 years	8
Radiology	3 years [2]	3
Oral Pathology	2 years	2

The Institutes also conduct residency training. Current approved residency programs are listed below:

Service	Institute	Approved	Residents Currently in Training
Internal Medicine	NHI [3]	1 year	6
Neurology	NINDB	2 year [4]	3
Psychiatry	NIMH	1 year	8
Dermatology	NCI	1 year	2

[1] Combined 4-year program in Clinical and Anatomical Pathology is offered.

[2] Approval is on a probationary basis until June 30, 1964.

[3] In June 1963 continued approval of Internal Medicine for the CC-NIH was given without mention of Institutes [clarification revealed that this approval now covers all Internal Medicine areas - NCI, NIAID, NHI and NIAMD] for one year of training credit. Dr. Donald Fredrickson has been named Director of the Internal Medicine Residency program.

[4] Effective July 1, 1964, approval is for one year.

B. The CORD Program

The Commissioned Officer Residency Deferment Program, developed and conducted by the PHS with the cooperation of the Selective Service System, permits a limited number of draft-eligible physicians (1) to become Inactive Reserve Officers in the PHS, and (2) to complete one or more years of formal residency training before serving on active duty. The mechanisms established in this program have been incorporated into the selection process for Clinical and Research Associates. Deferments are arranged by this office's representations to the PHS CORD Committee through official channels. The Chief of this Branch, a member of the Committee, participates in the deliberations on all NIH nominees.

C. The Clinical & Research Associate "Matching Program"

The Clinical and Research Associate Matching Program developed in 1958 provides an orderly, systematic method whereby the Institutes can select future junior staff members for appointment and deferment without inter-Institute conflicts and assures that our relations with young professional people will be on a dignified, fair, competitive basis. It is designed to minimize unproductive processing and interviewing of applicants. It also provides a method of recruitment for other positions in the PHS if candidates are not selected for appointment to NIH.

Clinical and Research Associates are selected by a system of matching the candidates' preferences against nominations made by the Institutes. Completed applications, including references, when filed with the Chief, Clinical and Professional Education, are photocopied and sent to each Institute to which the candidate has indicated he would like to apply. Program Chiefs of the Institutes review the applications and either reject the applicants or request this office to arrange interviews, which are held during a 3-week period in October. Following interviews, candidates indicate their preferences by Institutes and specific areas within Institutes. These are kept in confidence and used exclusively for matching against Institute nominations during the first week in November. Successful candidates are nominated for CORD Program deferment from obligated military duty while receiving residency training elsewhere until the effective date of their NIH appointment.

Statistics on Clinical and Research Associate Matching Program

Total inquiries ---------- 1833+
Non eligibles ---------- 21
Applications sent ---------- 833+
Files established ---------- 366
  Withdrew & non-eligible after filing applications --- 28
  Rejects before selection by Institutes ---------- 44
  Considered for appointment ---------- 293
  Interviews arranged ---------- 1983+
  Total appointed ---------- 166
    Clinical & Research Associates appointed --- 152
    Others appointed ---------- 14

For active duty in:

1964-----	10	1967-----	9
1965-----	126	1968-----	2
1966-----	18	1969-----	1

The following is an analysis of candidates considered by programs for which they applied:

Clinical Associates only---------- 110
Research Associates only---------- 35
Clinical & Research Associates ---- 177

The following is an analysis of candidates by Institutes to which they applied:

	TOTAL	CLINICAL ONLY	RESEARCH ONLY	BOTH
NCI	183	52	17	114
NHI	195	53	20	122
NIAID	142	25	13	104
NIAMD	188	39	18	131
NICHHD	20	5		15
NIDR	14	2	2	10
NIMH	80	14	14	52
NINDB	84	22	11	51
OIR	34		34	
CC-ANES.	5	5		
CC-RAD.	3	3		
CC-PATH.	2	2		

Further statistics are supplied in Attachment A.

At the conclusion of the calendar year 1963 program, the Scientific and Clinical Directors in an Ad Hoc meeting recommended that this office continue the policies and procedures of operation used in the program just concluded. [Schedule of the 1964 Calendar and Program Procedures was approved as set forth in Attachment B.]

Also under discussion at the Ad Hoc meeting was the question of whether or not use of the Matching Program by "fringe" areas might dilute the quality of the Clinical Associate and Research Associate Programs. No action was taken, but one possible solution suggested was that the difference in these positions be acknowledged and more appropriate terminology sought to differentiate from the bona fide Clinical Associate and Research Associate positions.

The brochure "Building Medical Research Manpower" has been revised and is now entitled "Opportunities for Clinical and Professional Education at NIH."

Again in February 1964, letters announcing the 1964 program (1966 appointments), enclosing schedule of deadline dates, were sent to the following:

Deans of Medical and Dental Schools
Presidents of Senior Class - Medical & Dental Schools
Chiefs of the following Services in hospitals:

Anesthesiology
Dermatology
Pediatrics
Internal Medicine
Radiology
Surgery
Neurology
Neurosurgery
Psychiatry

Since conclusion of the 1963 program the following changes have been recommended by the Scientific and Clinical Directors:

(1) A poster describing the NIH programs be prepared and distributed to the medical schools this year. (This was accomplished in June.)

(2) The various leaflets in the Clinical and Research Associate packet be consolidated into one complete brochure for the calendar year 1965 program.

Attachment A

The following tabulation is a representation of the Medical Schools from which candidates applied and from which we appointed candidates.

SCHOOL	APPLICANTS	APPOINTEES
Medical College of Alabama	5	1
Loma Linda Univ. School of Medicine	1	1
Univ. California School of Medicine, L.A.	3	2
Univ. California School of Medicine, S.F.	4	2
Univ. Southern California Sch. of Medicine	2	1
Univ. Colorado School of Medicine	3	3
Yale University School of Medicine	9	6
Georgetown Univ. School of Medicine	4	
George Washington Univ. School of Medicine	6	1
Univ. Florida College of Medicine	2	1
Univ. Miami School of Medicine	1	1
Emory University	3	
Northwestern Univ. Medical School	2	
University of Chicago	10	6
Univ. Illinois College of Medicine	2	
Indiana Univ. School of Medicine	2	
Chicago Medical College	1	
Univ. Louisville School of Medicine	1	1
Tulane Univ. School of Medicine	2	1
Johns Hopkins Univ. School of Medicine	20	9
Boston Univ. School of Medicine	2	
Harvard Medical School	42	33
Tufts Univ. School of Medicine	7	2
Univ. Michigan Medical School	7	3
Univ. Minnesota Medical School	1	
St. Louis Univ. School of Medicine	2	
Washington Univ. School of Medicine	3	1
Creighton Univ. School of Medicine	1	
Albany Medical College	2	
Albert Einstein College of Medicine	14	6
Columbia Univ. College of P&S	22	15
Cornell Univ. Medical College	11	5
Univ. Buffalo School of Medicine	1	
New York Univ. College of Medicine	22	6
State Univ. New York at Buffalo	1	1
Univ. of Rochester School of Medicine	8	5
State Univ. N.Y., Downstate Med. Center	13	4
State Univ. N.Y., Upstate Med. Center	4	1
Duke Univ. School of Medicine	14	10
Bowman Gray School of Medicine	2	1
Univ. Cincinnati College of Medicine	2	1
Western Reserve Univ. School of Medicine	9	7
Ohio State Univ. School of Medicine	1	1
Univ. Oklahoma School of Medicine	2	2

SCHOOL	APPLICANTS	APPOINTEES
Univ. Oregon Medical School	1	1
Hahnemann Med. College & Hosp. of Philadelphia	3	1
Jefferson Medical College	4	3
Univ. Pennsylvania School of Medicine	7	2
Univ. Pittsburgh School of Medicine	3	2
Vanderbilt Univ. School of Medicine	3	3
Baylor Univ. College of Medicine	3	2
Univ. Texas Southwestern Medical School	2	
Univ. Vermont College of Medicine	2	1
Univ. Virginia School of Medicine	6	1
Medical College of Virginia	1	
Univ. Wisconsin Medical School	4	2
Marquette Univ. School of Medicine	3	2
McGill University	2	1

The following tabulation is a representation of Hospitals at which candidates and appointees served their internships.

HOSPITAL	APPLICANTS	APPOINTEES
Univ. of Alabama Hospital	2	
Kaiser Foundation Hospital	1	1
Los Angeles County General	1	1
Palo Alto-Stanford Hospital	7	3
Univ. California Hospitals, L.A.	2	1
Univ. California Hospitals, S.F.	6	3
Santa Clara Co. Hospital	1	
Univ. of Colorado Hospital	1	
Grace-New Haven Hospital	9	3
Greenwich Hospital	1	1
D. C. General Hospital	1	
Georgetown University Hospital	2	1
George Washington Univ. Hospital	1	
Univ. of Florida Hospital	1	
Emory University Hospital	1	
Grady Memorial Hospital	1	
Queen's Hospital, Hawaii	1	1
Cook County Hospital	1	
University Chicago Clinics	4	3
Michael Reese Hospital	3	1
Univ. of Illinois R&E Hospitals	2	
Indiana Univ. Medical Center	1	
St. Vincent's Hospital	1	
Univ. of Kentucky Hospital	1	
Johns Hopkins Hospital	21	9
Univ. of Maryland	1	
Beth Israel, Boston	6	5
Boston City Hospital	13	9
Massachusetts General Hospital	18	13
Peter Bent Brigham	9	6

HOSPITAL	APPLICANTS	APPOINTEES
Boston Floating Hospital	1	1
Children's Hospital Med. Center	3	2
Mount Auburn Hospital	1	
Univ. of Michigan Hospital	5	3
Receiving Hospital, Michigan	1	
Henry Ford Hospital	2	
Ancker Hospital, Minn.	1	
Univ. of Minnesota Hospital	4	3
St. Louis Univ. Hospital	2	
Barnes Hospital	9	4
Jersey City Medical Center	1	
Bronx Municipal Hospital Center	10	5
Buffalo General	1	1
Bellevue Hospital	22	10
St. Vincent's	1	1
Kings County	5	
Presbyterian Hospital	6	5
Maimonides Hospital	8	4
Montefiore Hospital	2	1
Mount Sinai Hospital	6	1
New York Hospital	5	3
St. Luke's Hospital	3	2
Strong Memorial	8	3
Upstate Medical Center	4	3
Mary Imogene Bassett	1	
Albert Einstein Medical Center	1	1
Buffalo Children's Hospital	1	
Long Island College Hospital	1	
Duke University Hospital	19	12
North Carolina Memorial	2	
Cincinnati General Hospital	1	
Cleveland Metropolitan General Hosp.	2	2
Univ. Hospitals, Western Reserve	8	2
Mt. Sinai Hospital	1	
University of Oregon	4	4
Philadelphia General	2	
Univ. of Pennsylvania Hospital	6	1
Presbyterian Hospital, Phila.	1	1
Presbyterian Hospital, Pgh.	2	1
Einstein Medical Center	1	
Jefferson Davis Hospital	1	1
Parkland Memorial Hospital	1	
Vanderbilt University Hospital	7	7
Univ. of Utah Hospital	1	
Salt Lake Co. General Hospital	1	1
Mary Fletcher Hospital	2	2
Medical College of Virginia	3	2
Univ. of Virginia Hospital	4	2
Univ. of Washington Hospital	1	1
King County Hospital	2	2
Hadassah Univ. Hospital	1	

Attachment B

SCHEDULE CLINICAL & RESEARCH ASSOCIATE MATCHING PROGRAM
For Calendar Year 1964
(Appointments Beginning July, 1966)

January & February	Preparation of Packet Materials and Applications
March April May June July August	Receipt & Processing of Applications
Sept. 4	Final date for sending application forms to candidates
Sept. 13	Deadline for receipt of completed applications
Sept. 21 to Oct. 2	Review of applications by Institutes
Oct. 5 to 23	Scheduled interviews with candidates
Oct. 23 to 28	Selection of appointees by Institutes
Oct. 29	Matching
Oct. 30	Institutes notified of results of matching
Nov. 2	Inter-Institute negotiations and final approval of matching results
Nov. 3	Telephonic notification of successful candidates of selection for appointment
Nov. 4 to 11	Confirmation of appointment of all candidates by letter by Institutes; notification by Clinical & Professional Education Branch to unsuccessful candidates of their failure to be selected; release of unsuccessful candidates for recruiting by other programs; notification of Division of Personnel, OSG, regarding actions taken on all candidates.

CLINICAL AND RESEARCH ASSOCIATE "MATCHING PROGRAM"

The National Institutes of Health Clinical and Research Associate "Matching Program" came into being to meet a variety of problems and needs. Its most important elements are:

1. It provides an orderly, systematic method whereby the Institutes can appoint and defer future junior staff members without inter-Institute conflicts and with the assurance that our relations with young professional people will be on a dignified, fair, competitive basis.

2. It provides a method whereby candidates for opportunities at NIH can be actively recruited for other positions in the Public Health Service in the event they do not qualify or are not selected for appointment here.

3. It is designed to minimize unproductive processing of applicants and the consequent waste of NIH and Division of Commissioned Officer Personnel staff time.

PROCEDURES FOR OPERATION OF THE PROGRAM

I. Inquiries

All inquiries should be directed to the Clinical & Professional Education Branch, CC, for appropriate and coordinated action.

II. Actions Taken on Inquiries

A. Candidates in which NIH is not interested are sent the following:

1. Letter outlining requirements for appointment at NIH and stating candidate does not qualify on one or more points.

2. Letter discouraging applicant who minimaly qualifies but will not successfully compete(candidate is advised of other opportunities in the PHS).

B. Candidates of definite interest to NIH:

1. Inquiries may be answered directly by Clinical or Scientific Directors if they so desire, or they may be forwarded to this office for reply.

2. If inquiries are answered by the Institutes it is requested that a copy be sent to this office, so that a file card may be established. As candidates may apply to several Institutes simultaneously the above is very important to avoid duplication and to maintain continuity and coherence.

3. All "Matching Program Packets" are mailed by the Clinical & Professional Education Branch of the Clinical Center.

4. A master index card is established for every inquiry received.

5. All candidates for the Clinical & Research Associate programs will be required to complete the various information sheets contained in the Packet.

III. Actions Taken on Information Sheets (applications) Received

A. Upon receipt of the completed information sheets a file is established for each candidate and an application for deferment is sent to candidate.

B. When each file is complete (i.e. three letters of reference, and two copies of grade transcripts,) the material is photocopied (except grade transcripts) and sent to each of the Institutes to which the candidate has indicated he would like to apply. The Division of Commissioned Officer Personnel, PHS, is notified that an application has been received.

C. Attached to each candidate's file is a route slip asking for your action on the candidate; i.e. reject or arrange interview. This route slip when marked with your action is to be returned to this office.

D. A letter of reference will be requested from the "Chief of Service" of the candidate, if he has not already submitted one.

E. Grade Transcripts will not be duplicated with the files, but will be maintained in a master file in this office. They will be sent on loan to the Institutes upon request.

F. Final date for sending application forms to candidates, September 4, 1964.

G. Deadline for receipt of completed applications is September 13, 1964.

H. Photographs are requested from interviewed candidates and are kept in the master file in this office for use by Institutes.

IV. Interviews

A. All interviews are by invitation only and are to be arranged only by the Clinical and Professional Education Branch, Clinical Center.

B. The Clinical & Professional Education Branch of the Clinical Center will notify all candidates of the date of their interviews and the Institutes that wish to interview them.

C. All interviews will be held during the three week period October 5 thru October 23, 1964.

D. All persons in the Institutes who will be interviewing candidates will be asked to inform this office the days of the week and the hours that they will devote exclusively to interviews during the above three week interview period.

E. Each person interviewing candidates will be sent a weekly interview schedule marked off in half-hour blocks for each day. As interviews are arranged each interviewer will receive a memorandum giving candidate's name, date of interview and time. Please be sure that this information is put on the weekly schedule.

F. Each candidate will be given a detailed interview schedule listing time, Institute, Interviewer, and location of interview, when he reports to this office the day of his interview.

G. If you desire to have a candidate interviewed by another person within your Institute, please check his schedule and that of the candidate to be sure time permits.

H. If you think a candidate should be interviewed by a person or persons in another Institute please check with this office before making these arrangements. This is necessary because: The candidate may have applied to this Institute; his file will have been reviewed by persons in this Institute; if the Institute is not listed on his interview schedule it means they are not interested in a person with his background and qualifications. If you still feel that the candidate should be seen please make arrangements thru the Clinical or Scientific Director of the Institute.

I. No candidate is to be offered a position at the time of interviews.

J. When the candidate has completed his interviews he will return to the Clinical & Professional Education Branch and fill out a rank order sheet listing Institute and Laboratory or Section, if this is necessary, within the Institute. This is a confidential statement.

V. Selection, Matching and Notification of Appointees

A. By October 28, Institutes will submit, to this office in writing, a rank order list of the candidates they wish to appoint. This list should contain at least twice the number of candidates needed for your positions.

B. The rank order lists of the Institutes will be matched with the candidates rank order sheets.

C. On November 2, Institutes will be notified by telephone of the results of the matching.

D. If an Institute has chosen a candidate for appointment and the candidate has not listed the Institute, or Section within an Institute, on his rank order list and has not been selected by one he did list, the Institutes will be given this information and two courses of action may be taken:

    1. The Institute can select another appointee.
    2. The Institute may offer the position to the candidate to see if he is interested and will accept.

E. On November 3, the Institutes will, by telephone, offer their appointees the positions for which they were selected (subject to approval of their nomination for CORD deferment, if this is involved) and ask for a verbal acceptance. If the Institutes wish, the telephone call may be followed up with a letter of appointment.

F. If an "appointment letter" is <u>not</u> to be written, at the time of the telephone call, the Institutes should ask for a letter of acceptance from the candidate. In any event we must have a letter of acceptance from each candidate, whether or not an appointment letter is written.

G. If an "appointment letter" is written the acceptance letter can be requested at that time.

H. Two copies of the appointment and acceptance letter on each appointee must be sent to this office.

I. Rejection letters to all unsuccessful candidates will be mailed by this office on November 4.

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER
OFFICE OF THE DIRECTOR

DEPARTMENT OF SPIRITUAL MINISTRY

CC-09
Serial No.

OVERVIEW:

In keeping with the Clinical Center's goal to bring the best that modern medicine and its ancillary services have to offer to the care and rehabilitation of the patients, it is recognized that the spiritual welfare of the patient is an important factor in the care of the sick. Meeting the spiritual needs of individual patients is the primary mission of the chaplains on the Clinical Center staff.

During the last 18 months there have been a number of changes in personnel. Chaplain William Andrew, Supervisory Chaplain, resigned June 14, 1963 after eight years of service. Chaplain LeRoy G. Kerney was appointed the new Supervisory Chaplain on September 3, 1963. Father Francis Veith, the Roman Catholic Chaplain, resigned on May 30, 1963 after having served for about seven years at the Clinical Center. He was replaced by Father John McFee who served until Father William O'Donnell joined the department on January 17, 1963. Father Armand J. Guicheteau entered on duty June 1, 1964 and is the current Roman Catholic Chaplain.

Major emphasis, during this period, has been to continue the current patterns of spiritual ministry to the patients and to lay the foundation for a much needed and hoped for expanded program of excellent patient ministry, possible educational programs, and research opportunities.

CHAPEL SERVICES:

Regular Chapel Services were held during the year by the various Chaplains. These services were:

PROTESTANT: Sunday, 10:00 a.m., a Holy Communion Service the first Sunday of each month.

CATHOLIC: Sunday, 7:15 a.m. and 8:30 a.m. and Weekdays, 7:00 a.m. Daily distribution of Communion to bedridden patients.

JEWISH: Friday, 1:30 p.m.

In addition to these regular services, special services were also held, which include:

PROTESTANT:
- Good Friday Service
- World Wide Communion - 1st Sunday in October
- Thanksgiving Day Service
- Christmas Eve Carol Service

CATHOLIC:
- Stations of the Cross - during Lent
- Distribution of Ashes (Ash Wednesday)
- Daily Rosary Services - during the months of October and May
- Christmas Eve Mass

JEWISH:

Rosh Hashanah	Purim
Yom Kippur	Passover
Sukoth	Shavuoth
Chanukah	

It is interesting to note that on the same day, March 27, 1964, the following services were held: a Daily Mass at 7:00 a.m. and Stations of the Cross at 11:30 a.m.; a Protestant Good Friday Service from 12:30 - 3:00 p.m.; and a Jewish Passover Service at 1:30 p.m. in the General Assembly Hall.

Special Memorial Services were held for President Kennedy on November 25, 1963 at the Clinical Center for the three faith groups, with a total attendance of 330. A wedding was solemized in the Chapel of a Protestant patient who was unable to leave the hospital. Funeral services of three staff members of NIH, and three patients were conducted by the Protestant Chaplains at nearby funeral homes.

WARD MINISTRY TO PATIENTS AND THEIR FAMILIES

Most of the work of the chaplains is carried out on the various nursing units with individual patients and their families. The pattern of ministry of the chaplains vary according to their own traditions. Pastor, Priest, Rabbi each have their unique approach to meeting the spiritual needs of their patients. All the chaplains minister to relatives as well as to individual patients, consult and confer with staff members, and are available for emergencies on a 24 hour basis.

Differences in the ministry to individual patients by the various chaplains varies according to the ratio of patients to chaplains. The Roman Catholic Chaplain is responsible for an approximate average of 80 patients on any given day. The two Protestant Chaplains are responsible for an approximate average of 300 patients. Since Chaplain Kerney also has administrative duties as the Supervisory Chaplain, the ratio of patients to chaplain is closer to one chaplain to 200 patients. The Jewish Chaplain serves on a part-time basis. He is responsible for approximately 30 patients at any given time.

ORIENTATION TO STAFF:

The Protestant and Catholic chaplains have been a part of the monthly orientation program for nursing personnel, discussing the role of religion in the clinical center, the work of the chaplains, and details of the various services and approaches of the three major faiths. Chaplain Kerney and Father O'Donnell participated in orientation sessions for the Gray Ladies, new social workers, a new AOD, and the head nurses. Chaplain Kerney and Father O'Donnell have attended staff conferences on 2-East. The Chaplains, on occasions, have made "rounds" with the various staff doctors, and have attended a number of clinical conferences.

PROFESSIONAL MEETINGS:

The Protestant and Catholic chaplains have attended a monthly seminar conducted by the chaplains of the Navy Hospital. Topics discussed included:

"Some General Considerations about Cancer and the Cancer Patient"
"Faith Healing"
"Group Therapy"
"Sacraments of the Sick Room"
"The Patient's Right to Die"
"Verbatims as a Tool of the Hospital Chaplain"
"Clinical Pastoral Education and the Hospital Chaplain"

Chaplains Kerney and White attended the third annual Davison Lecture on Religion and Medicine, sponsored by the Committee on Liaison with the Clergy of the Medical Society of the District of Columbia.

Chaplain Kerney attended the Fall Conference of the Council for Clinical Training at Indianapolis, Indiana, and a panel discussion on Paramedical Activities at the Washington Hospital Center. Chaplain Kerney has attended a meeting of the Washington Academy of Religion and Mental Health, of which he is a member.

COMMUNITY CONTACTS:

The various community contacts by the chaplains are too numerous to list. They include attendance at ecclesiastical meetings, Council of Church meetings, and contacts with various church leaders of the community. From time to time, various pastors have come by the offices to become acquainted and to be helped in their ministry to their parishioners. A number of chaplains in the area have paid a visit to the Clinical Center including a minister from England.

Chaplain Kerney gave the invocation at the Federal Hospital Executives Luncheon, the Graduation Exercises for the Gray Ladies of the area, and at a United Fund Luncheon for key men of Federal Agencies. Chaplain White gave the invocation and benediction at the Graduation Exercises for High School students in the Gray Ladies Volunteer Program.

LECTURES:

Chaplain Kerney gave the following lectures:

"The Relationship of Psychotherapy and Religion", New York Avenue Presbyterian Church, Washington, D.C.
"Christian Faith and Family Living," a series of six lenten seminars at St. Mark Presbyterian Church, Bethesda, Maryland.
"Ministry to the Physically Ill," Wesley Seminary, Washington, D.C.
"Clinical Pastoral Education and the Hospital Chaplain," National Navy Medical Center, Bethesda, Maryland.

Chaplain White was a panel discussant at Children's Hospital on the topic, "The Care of Children with Malagnancies." The Institute was sponsored by the Maternal and Child Health Council of the D.C. League for Nursing.

FUTURE OBJECTIVES:

At the current time, the Protestant ministry to patients is limited to largely an "emergency" ministry. In order to move to a program of excellence in patient ministry it would be necessary to expand the number of Protestant Chaplains. The addition of two Protestant Chaplains will help to give coverage beyond the "emergencies" that arise and to bring into line an equal ratio of patient to chaplain among the three faith groups. A ratio of one chaplain to 80 patients is seen as a minimual basis for a program of excellence in patient ministry.

It is hoped that appropriate programs of education and research can be explored and developed that would enable the department of spiritual ministry to carry out the major goals of the Clinical Center.

PROTESTANT CHAPLAINS:

I. Chaplain Kerney, who also serves as Supervisory Chaplain spends half of his time with administrative duties.

Helping the patient as a person to find meaning and courage in the face of chronic illness and death requires individual attention. This is time consuming. Because of the limitation of staff, the Protestant Chaplains find it necessary to concentrate their services mainly on the very sick and critically ill. From these visits, contacts are made with roommates and through referrals by doctors, nurses, social workers, relatives and others.

The Rev. Thomas Allen, minister of the St. Luke's Episcopal Church in North Bethesda, and the Rev. James Macdonnell, minister of the St. Mark Presbyterian Church, North Bethesda, serve as "On Call" Chaplains for emergencies.

II. General Summary of Services Provided by the Protestant Chaplains

1. Protestant Chapel Services for Patients, relatives and friends on Sunday at 10:00 a.m. A Holy Communion Service is held the first Sunday of each month.

2. Special religious services - Thanksgiving, Good Friday, World Wide Communion Sunday, Christmas Eve Carol Service.

3. Bedside Communion upon request from the patients.

4. All seriously ill patients are visited.

5. All surgical patients are seen prior to surgery and are followed up.

6. Chaplains meet with the family of deceased patients at the time of death, unless there is no family or the family has their own minister.

7. At least one third of the ministry of the chaplains is to the families of the patients, i.e. during surgery, death situations, serious illness.

8. Religious literature is made available to patients upon request.

9. Consultations with medical, nursing and social work staffs regarding welfare and rehabilitation of patients.

10. Participation in orientation program for all new Nursing and Social Work Staff.

11. Participation in programs of the Patient Activities Section.

12. Participation in the Gray Lady Training Program.

13. Consultation with members of the N.I.H. staff on request.

14. On call for emergency service 24 hours a day.

THE CLINICAL CENTER
NATIONAL INSTITUTES OF HEALTH
Bethesda, Maryland

PROTESTANT CHAPLAIN'S ACTIVITIES FOR January, 1963 through June, 1964

1. WORSHIP SERVICES

Chapel Services	78
Sermons	78
Attendance	5,116
Average	67

2. ADMINISTRATION OF SACRAMENTS

Holy Communion	18
Chapel	625
Bedside	190
Baptisms	3

3. PASTORAL MINISTRY

Initial Religious Contacts	1,531
Surgery	2,622 visits
Seriously Ill	3,457 visits
Counseling	4,682
Rounds	2,051
Relatives	6,689
Deaths	120
Funerals	3
Post Discharge	114

4. PATIENT REFERRALS

Doctors	192
Nurses	697
Social Workers	471
Clergy	37
Family	174
Self	107
Other	26

5. STAFF RELATIONS

Conferences	4,127
Staff Meetings	34
Lectures	34
Counseling	43

6. COMMUNITY

Clergy Contacts	392
Addresses	7
Services	4
Meetings	36
Professional Conferences	6

7. ADMINISTRATION

Correspondence	296
Planning (hrs.)	424
Conferences	977
Study (hrs.)	707-1/2
Records & Reports	237

8. OFF-DUTY CALLS

Emergencies	88
Overtime (hrs.)	249

9. PERCENT OF PROTESTANT PATIENT POPULATION SEEN — Approx. 35 to 40%

CATHOLIC CHAPLAIN

1. The religious needs of the Catholic patients at the Clinical Center are provided for by one Catholic Chaplain on full-time basis. The Catholic patient census continues to maintain an average of 20% of the total patient census, which amounts to an average of 75 to 80 patients.

The Catholic Chaplain's ministry begins with hearing confession and distributing Communion to the patients. His ministry broadens out from these contacts to include pastoral counseling, instruction, work with families and consultation with staff members. Although priority is given to patients and their families, a significant amount of time is devoted to work with hospital personnel.

Services provided by the Catholic Chaplain at the Clinical Center are summarized below in a general manner, followed by a detailed statistical summation of daily activities.

II. General Summary of Services Provided by the Catholic Chaplain

1. Divine Worship Service (Mass) for patients, relatives, and N.I.H. personnel daily. (Two services on all Sundays and Holydays).

2. Special religious services daily during months of May and October.

3. Special religious services during seasons of Advent and Lent.

4. Sacraments administered to patients daily.

5. All patients visited each Saturday for confession.

6. Seriously ill patients visited every day.

7. Weekly consultations with families of patients.

8. All patients visited on regular schedule for counseling.

9. Consultations with Medical, Nursing and Social Service staffs regarding welfare and rehabilitation of patients.

10. Participation in orientation program for all new Nursing and Social Service personnel.

11. Participation in programs of the Patient Activities Section.

12. Participation in the Gray Lady Training Program.

13. Consultation with members of the N.I.H. staff on request.

14. On call for emergency service 24 hours a day.

THE CLINICAL CENTER
NATIONAL INSTITUTES OF HEALTH
Bethesda, Maryland

CATHOLIC CHAPLAIN'S ACTIVITIES FOR January, 1963 through June, 1964

1. WORSHIP SERVICES

Services	642
Attendance	15,268
Sermons	68
Devotions	33
Attendance	2,061

2. ADMINISTRATION OF SACRAMENTS

Holy Communion	13,395
Chapel	7,963
Bedside	5,432
Confessions	988
Baptisms	4
Confirmations	4
Last Rites	107

3. PASTORAL MINISTRY

Initial religious contacts	1,563
Surgery	693 visits
Seriously Ill	1,860 visits
Counseling	2,466
Rounds	4,026
Relatives	802
Instructions	19
Deaths	61
Funerals	1
Post-Discharge	42

4. PATIENT REFERRALS

Doctors	331
Nurses	756
Social Workers	79
Clergy	72
Family	312
Self	329
Other	17

5. STAFF RELATIONS

Conferences	123
Staff Meetings	11
Lectures	16
Counseling	509

6. ADMINISTRATION

Correspondence	166
Planning (hrs.)	16-1/2
Conferences	18
Study (hrs.)	52
Records & Reports	58

7. COMMUNITY

Clergy Contacts	15
Addresses	3
Meetings	4
Professional Conferences	4

8. OFF-DUTY CALLS

Emergencies	15
Over-time (hrs.)	715

9. PERCENT OF CATHOLIC PATIENT POPULATION SEEN 100%

JEWISH CHAPLAIN

Jewish chaplaincy service is on a contract basis providing for 12 visits per month. Rabbi Joseph M. Brandriss has been serving as Jewish Chaplain since November 27, 1956. Approximately 8% of the patients admitted to the Clinical Center are Jewish.

Summary of Service

Sabbath services on Fridays and special services for the various major and minor Holidays of the Jewish calendar, including some socials after the celebrations.

Visits to patients.

Counseling of patients and families.

Religious education when requested and/or needed.

On call for emergency service 24 hours a day.

THE CLINICAL CENTER
NATIONAL INSTITUTES OF HEALTH
Bethesda, Maryland

JEWISH CHAPLAIN'S ACTIVITIES FOR January, 1963 through June, 1964

1. WORSHIP SERVICES

Chapel Services	62
Sermons	51
Attendance	366
Average	6

2. SPECIAL JEWISH HOLIDAY SERVICES

Services	11
Sermons	10
Attendance	291

3. PASTORAL MINISTRY

Initial Religious Contacts	250
Surgery	47
Seriously Ill	72
Counseling	30
Rounds	362
Relatives	240
Deaths	10
Funerals	1
Post-Discharge	

4. PATIENT REFERRALS

Doctors	9
Nurses	21
Social Workers	11
Clergy	1
Family	21
Self	3
Other	2

5. STAFF RELATIONS

Conferences	8
Staff Meetings	
Lectures	
Counseling	

6. COMMUNITY

Clergy Contacts	
Addresses	
Services	
Meetings	
Professional Conferences	

7. ADMINISTRATION

Correspondence	32
Planning (hrs.)	12
Conferences	8
Study (hrs.)	6
Reports & Records	6 hrs.

8. OFF-DUTY CALLS

Emergencies	4

9. PERCENT OF JEWISH PATIENT POPULATION SEEN 100 %

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER
ADMINISTRATIVE BRANCH

EMPLOYEE HEALTH SERVICE BRANCH

CC-12
Serial Number

Major Service Activities

Emphasizing preventive rather than therapeutic medicine, the NIH Employee Health Service provides the following occupational health services to NIH employees.

1. Preventive medical services to maintain optimum health and productivity, such as immunizations, periodic chest X-rays, and other multiphasic screening procedures.

2. Prevention and control of environmental health hazards such as infectious disease surveillance, periodic blood studies for the effects of toxic chemicals, and cooperative activities with safety personnel.

3. Management of occupational injuries and diseases and other medical emergencies that occur on the reservation.

4. Health counseling and guidance in cooperation with employees' private physicians.

Acting as the focal point for all matters relating to the health of employees, the Employee Health Service recognizes a dual responsibility to serve both the health needs of management and those of employees. Management shares in the benefits of the program through efforts to control sickness absenteeism and occupational disease hazards with resultant increased research output and working efficiency. At the same time, employees benefit as a result of our efforts to maintain their health at an optimum level through the provision of accepted preventive health measures.

Major Accomplishments

Infectious disease hazards, originating both in the laboratory and through patient-care exposures, have continued to receive our careful attention. A new and expanded program to provide needed immunizations has been undertaken with the Division of Biologics Standards during the past

year. Because the hazards themselves vary as the research projects progress, immunizations and periodic chest X-rays have been extremely difficult to schedule. We are hopeful that the new system, which requires close cooperation between administrative, professional, and safety personnel, will insure improved employee acceptance and participation. It is also hoped that the project with DBS will provide the experience and framework for improving programs in other areas where the problem exists.

Emphasis has been placed during the past year on improving health protective measures for animal caretakers, particularly those involved in the Animal Hospital, Animal Quarantine and sub-human and primate activities. The pre-exposure rabies immunization program, utilizing duck embryo material, has now been firmly established, concentrating only on employees in the Dog and Cat Quarantine Unit because of the rigid enforcement of quarantine regulations, which have reduced to an absolute minimum the rabies hazard for all other employees. The tuberculosis hazard from sub-human primates is carefully controlled through provision of periodic chest X-rays for employees and tuberculin eye test for primates. The potential, yet very real hazards of chimp-borne infectious hepatitis is being managed through provision of gamma gloublin at 3 month intervals in small doses to employees so exposed. The highly virulent, but fortunately rare, B Virus infection of sub-human primates is kept under constant surveillance and requires the EHS staff to remain alert to treat all monkey bites with extreme care.

During the year, a completely new system of managing Bureau of Employees Compensation records has been inaugurated. CA-1 forms, "Notice of Injury", formally filled out by our nurses and signed by the employee, are now more correctly filled out completely by the employees. Other reporting forms have been simplified and the legal rights of employees and management are now more adequately protected.

An auxiliary Health Unit for Building 13 has been approved and construction is expected to begin soon. Upon completion of this Health Unit, the Employee Health Service will be more readily available to Plant Engineering and other supportive personnel whose duties and work responsibilities make them more liable to occupational injuries.

Each year we attempt to select a relatively common health problem among employees, one that is usually difficult to manage, and attempt to approach the problem through preventive medical means. The problem of obesity and weight control has been attacked aggressively during the year with the assistance of the Clinical Center Nutrition Department which has provided guidance and consultation. To date, 39 employees have had one or more consultations with Clinical Center Nutritionists with an encouraging number of successes to date. The program has not been in operation long enough to determine its long-term value.

Significant Contribution to Research Program

Our significant contributions to research programs would be those intangible benefits that would accrue from the improved and well maintained health that we hope our preventive medical programs produce for NIH staff

members. Concretely, however, we have also recognized opportunities to assist scientists in the selection of suitable clinical research material from within the stable NIH employee population. We have participated in many projects during the year in which employees have been used both in study projects and as normal controls. We have performed screening and referral functions for the NIAID study on respiratory viral diseases, the NIAMD study on the effect of respiratory viral diseases on blood clotting mechanisms, the NIAID study attempting to use the newer tissue culture techniques investigating the viral etiology of infectious monomucleosis, the NIH study on hypertension, various NIDR studies on dental problems, the Clinical Center Blood Bank hepatitis follow-up among employee donors, and the Clinical Center Radiation Safety Branch study on the determination of body potassium through whole body radiation counts. In assisting scientists to acquire suitable research subjects among employees, we recognize the necessity of the employee continuing to perform the full duties of his position without disrupting the orderly progression of work within his section. In addition, we believe that all research projects on which we collaborate, should benefit both the employee and the over-all NIH program.

Major Problems Encountered

Complete understanding of the role and function of the Employee Health Service, and the legal and administrative limitations under which it operates, has not been accomplished. Because we do not provide total medical care and must therefore limit the extent of our medical services, expressions of discontent or dissatisfaction continue to arise when employees are not given all the services which they would like to receive. Informal question and answer sessions have been held with the NIH Personnel Officers and this has helped to raise the level of understanding. We will continue to make every effort to carry out our responsibilities in a consistent and uniform manner, following documented policies and procedures, in the hope that this too will improve our acceptance both by management and staff. In an effort to improve our image, we are considering recommending a name change for our activity to Occupational Health Service, instead of Employee Health Service, as many of the NIH staff object to being called "employees."

Proposed Future Objectives

We are continually faced with the necessity of undertaking epidemiological studies on suspected occupational diseases, in addition to infectious diseases in patients which possibly could be traced to employee origins. Our present record system, basically a chronological accounting of individual employee medical problems is completely unsuited to these necessary epidemiological studies. We are in urgent need of a complete modernization of our records management and are investigating the feasibility of utilizing computation and data processing techniques. Having a more precise knowledge of the morbidity status of the employee population will assist us in directing our preventive medical efforts in a more scientific manner, and hopefully will direct our attention to areas in which potentially serious occupational disease hazards may exist. In addition, we hope to utilize machine tabulation techniques in the scheduling

of periodic chest X-rays and immunizations among those employees who require these to insure that they are receiving adequate health protection.

The number of employees reaching retirement age is steadily increasing as would be expected since NIH is advancing in years of operation. We are investigating the possibility of sponsoring, or at least contributing to, a retirement counseling program designed to assist the employee who is planning to retire in the coming year, to adjust to his new way of life. We consider this preventive medicine in much the same manner that the pediatrician assists his young charges in preparing them for adulthood.

The major health problem which requires our greatest attention is in the general field of mental health. We are hopeful that we can extend our efforts to apply sound preventive medical techniques in the early diagnosis of mental health problems. We feel that we will need considerable professional guidance and direct assistance and therefore are hopeful that our budget request for a staff psychiatrist will be implemented. Finding the problems is relatively simple; knowing what to do with them poses the serious problems. Control of the drinking problem and rehabilitation of the alcoholic is one example of un-met needs in the mental health field, and one which demands our increasing attention.

A series of regular noon time movies on health education and allied subjects is being organized in cooperation with the Training Section of the Personnel Management Branch. There is a vast amount of material available through the information offices of the various Institutes and we feel that all NIH employees should have this valuable health education material made available to them periodically during their lunch periods.

Selected Statistics

	FY 1964	1963	1962	1961
Total visits.....	27,035	25,653	25,208	22,798
Visits for occupational injuries and diseases.....	2,349	2,544	2,478	2,355
Immunizations.....	10,188	8,475	10,749	9,918
Pre-emp. physical examinations.....	2,744	2,880	2,886	2,094
Laboratory examinations.....	17,782	18,489	18,738	16,392
Referrals to personal physicians.....	1,440	1,757	1,934	2,359

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

SOCIAL WORK DEPARTMENT

CC-31
Serial No.

1963, the tenth anniversary year of the Clinical Center and its Social Work Department, was most productive in terms of the Department's ability to extend social work services to more patients and to publish observations about the social functioning of certain patient groups in medical and social work journals.

The recruitment of eight social workers, four with considerable experience and four recent graduates, enabled the Department to replace workers who had resigned and to fill positions vacant for some time.

During this year, a statistical system was devised to reflect the nature of the major medical social problem with which the patient and social worker were concerned as well as a numerical count of patient, family and supporting interviews. This device facilitates the Department's ability to keep abreast of changes in the nature of the patients' problems occasioned either by a complete change in or by a revision in research protocols. More precise knowledge of the nature of the patients' major problems in social functioning in a particular Institute, and the variety of problems within an Institute's program, aids in making appropriate worker assignments and in adapting social work skills to distinctive patient groups.

The Patient Welfare Fund continues to be a source of concern. While the amount and comparative proportion of the sources of income remain stable, the needs of certain categories - for example, family maintenance - continues to mount. Constant vigilance over expenditures and the cooperation of the Recreation and Welfare Association, the NIH Record and the NIH staff help the Department to maintain a minimally sufficient income.

The revision of the Clinical Social Work Series - 185 is imminent. As presently formulated by the Civil Service Commission, the revision eliminates specialization, in line with present thinking in social work education, and it provides a Welfare Series from which to recruit a social work assistant (technician) when appropriate.

Within the professional Social Work Series, it specifies a journeyman position at the GS-11 and a supervisory position at the GS-12, thus enabling the Federal social work programs to be competitive with private health and welfare agencies in recruiting the advanced social work practitioner. It also makes possible the reclassification of specialized positions in community organization, group work and research.

The staff development program has been diversified to meet the needs of staff at various levels of experience and with a breadth of professional interests. Foremost among the developments has been the addition to staff of a full-time social work researcher who offers both research consultation and instruction in research methodology to staff members. The orientation program and casework workshop are designed to meet the needs of less experienced staff. A seminar in working with children in hospitals was offered for the total staff to enlarge perceptions and skills in an area of increasing importance at the Clinical Center.

PATIENT CARE

NCI Social Work Section

Changes in the treatment and research focus on NCI resulted in changes in the social work program.

Endocrinology shifted from a predominantly homogenous group of young women patients to a heterogenous group, including both sexes and all ages. Particular attention is being paid to sexual precocity in children from five to ten and lack of sexual development in adolescents. School difficulties, accompanying social adjustment problems, and the need for vocational planning are the constellation of problems presented to the social worker by these patients.

The Surgery Branch has been characterized by an increase in numbers and in the diversity of surgical procedures. The trend has been to accept fewer cases in the later stages of cancer, resulting in the accelerated need for postoperative rehabilitation planning, particularly vocational retraining.

On the Solid Tumor and Chemotherapy Unit, a special study of Hodgkin's Disease has resulted in a homogenous group of patients within the unit. In the latter instance, psychiatric consultation has been regularly available to the total staff and provided a valuable assist to the hospital team in planning for the hospital adjustment and eventual life readjustment of a challenging group of patients.

A change in treatment method on the Children's Leukemia Unit required that the children be hospitalized for treatment during period of remission. Consequently, children were hospitalized for longer periods

of time, creating additional stress for them and increased pressures for their parents and the hospital staff. The increased length of stay was reflected in rising expenditures for the maintenance of parents who had no other source of funds.

In addition, in July 1963, eleven beds on 13-East were allocated for leukemic adolescents. In response to the pressing needs of these children, Mr. Joel Vernick initiated a demonstration group work program on 2-East with particular emphasis on the life space interview. The caseworker, Mrs. Maguire, continued to work with the parents. As the number of older children increased, Mr. Vernick shifted his base of operation from 2-East to 13-East. His focus has been to utilize the everyday incidents of life on the Unit and opportunities occasioned during the children's outings with him to help them talk about and deal with the unusually difficult experiences they are having in relation to the demands of their own illness and their knowledge of the illness of the other children. Mr. Vernick presented his observations about his work with these children at the Southwestern Regional Institute in San Francisco in October 1963. He also had the opportunity to discuss his experience with two outstanding child therapists, Mrs. Emma Plank, Western Reserve University, and Mrs. Selma Fraiberg, University of Toledo.

In addition to the direct work with the children, Mr. Lawrence Burke, caseworker on 13-East, and Mr. Vernick have jointly interviewed the parents and children around problems of mutual concern.

Undoubtedly, the Children's and Adolescent's Leukemia Units constitute an unusually difficult and challenging assignment for each member of the hospital team. The impact of fatally ill children; complex and often uncomfortable treatment procedures; parents away from home and under severe stress, both emotional and financial, are the combination of problems faced by the whole staff.

Foremost among the recommendations for easing the children's stay is the establishment of a facility for the parents who need to be here and for the families of other seriously ill patients. Short of this goal, there is a need for some appropriate recreational outlets for the mothers whose environment here is circumscribed by the hospital unit and the boarding house from which they are encouraged to leave as early as possible in the morning. Presently, volunteer efforts by the YWCA and the Grey Service have been helpful in the concerted staff effort to ease life on the unit by attention to these factors.

The social workers in the NCI section are also interested in preparing a pamphlet for the families which will help to anticipate and plan for the families' tangible and intangible needs for social work services.

The question of adequate coverage for the NCI clinics was resolved by the initiation of a demonstration project conducted by Mrs. Vincenza Bowles.

The study indicated a small incidence of referrals and it is to be questioned if a separate worker might be justified even on the basis of numbers alone. Because of the low incidence of clinic referrals (average of 1 every 3 days) and because most of the patients have been known previously to the Social Work Department, it would appear that the worker on an individual service could carry the referral load from clinic without greatly increasing overall work-load. If it is also considered that follow-up care is an integral part of total medical care, then the low incidence and relationship factor taken together would seem to indicate a need for consideration of house and clinic follow-up remaining the responsibility of the worker assigned to the service full-time. The one exception to this was previously mentioned, those patients who are seen in clinic only and who were to remain as out-patients only.

It was decided, as a result of this study, that the social workers responsible for the in-patient service would visit the clinics at each session in order to find out if there were patients who needed social work help. We plan to continue this approach for an evaluation period. If continuous visits to the clinics result in more referrals than the social worker can handle, we will again consider the possibility of assigning a worker to the clinics per se. Presently, the funds budgeted for the clinic social worker are being used to provide a full-time worker, Miss Barbara Feroe, for the 12-W Solid Tumor Unit.

NHI Social Work Section

In this Section it has become increasingly evident that the Institute is comprised of two contrasting groups, i.e., the swift-moving Cardiology and Surgery Branches (with the largest bed allocation), and the more slowly-paced Experimental Therapeutics, Clinical Endocrinology, and the Lipid Metabolism Branches.

With the continued growth and development of the Cardiology and Surgery Branches since 1960, various methods and staffing patterns have been initiated by the Department.

Upon the arrival of Miss Karen Schulman and Mrs. Ellen Lee, it was decided that they would share responsibility for the Cardiology Branch and would follow through with those patients who were transferred directly to the Surgery Branch during their hospitalization, as contrasted with those given return admission appointments. Miss Peay would have responsibility for all other surgical patients. In addition, Miss Peay held weekly meetings with the two new staff members for the purpose of facilitating their integration into the Medical and Surgical Units.

In March of this year, it was decided that relating to two separate Branches posed some difficult problems and, in view of this, it was decided to provide the opportunity for Mrs. Lee and Miss Schulman to divide the caseload and work only with those patients on the Cardiology Branch. All surgical patients would be followed by Miss Peay, except for those whose transfer would not be indicated based on casework evaluation and planning. Dr. Eugene Braunwald suggested that it would be helpful for the workers to be prepared to present material at daily afternoon rounds. This plan has been in effect since March 1964, and

the sharing of ideas and information has proved beneficial to the operation of the medical/research program.

Miss Peay's paper relating to social work on these Units - "What Social Service Offers to Patients Who Undergo Cardiac Surgery" was published in Public Health Reports in December, 1963.

Mrs. Dorothy Kuhl resigned her position as caseworker on the Clinical Endocrinology Branch in September, 1962, and since that time, this Unit has had social work coverage on a referral basis only. The Program Supervisor carried this responsibility until this January (1964), when Mr. Callagy, whose basic assignment is with Experimental Therapeutics Branch, began coverage of the Endocrinology Branch. The timing was propitious since there have been fewer patient admissions on the Experimental Therapeutics Branch during the past several months. Inability to cover all of this Section with full social work participation is considered critical, particularly since Dr. Bartter has always been one of our most enthusiastic supporters. The lack of continuity over the years in terms of social work participation with this group of patients has been serious, and it is one of the sections with a high potential for development. Mr. Callagy is now working with eight of the Endocrinology patients, and generally his caseload on Experimental Therapeutic Branch averages around 20 or 21 patients. An important recruitment factor for the Endocrinology Branch has been that we are unable to compete with private agencies in terms of salaries for experienced social workers. The reclassification of the Clinical Social Work Series will be of great assistance in recruiting for the Metabolic Unit.

Miss Barbara Murphy has been working with Mrs. Vincenza Bowles and Dr. Geraldine Conner to develop a research project to learn whether there is a change in the patients' social functioning following cardiac surgery. The study will be focused on children and it reflects Miss Murphy and Miss Peay's concern as well as a general trend and concern in the field of social work in Cardiology.

NIAMD Social Work Section

Mrs. Myrna Weissman observes two trends in her work on the Metabolic, Endocrinology, and Hematology services. The first is an increase in the use of her help in pre-admission planning. A second trend of interest has been the division of her caseload almost exclusively into two patient groups. Elderly people, primarily from the Metabolic Service, with the geriatric problems of retirement, loneliness, unsatisfactory living arrangements compose one group; the other consists of young adults, who because of illness, have never had an opportunity to establish themselves independently. They need help, not with social re-entry as do so many of our chronic disease patients, but with social entry -- vocational planning, finding appropriate living situations, developing community ties.

On the Arthritis Service, Miss Barbara Spillman has been able to extend her coverage so as to offer screening interviews to nearly every patient admitted to this service. Through her contacts with nurses and through the medium of medical rounds, she is able to keep in close touch with the Pediatric Metabolic Service and is initiating an increasing number of contacts with parents and with the young patients themselves.

NIAMD has continued to admit a number of children and they have been one of the Social Work Section's principal areas of work and concern. Miss Spillman has been working particularly with several of the youngsters with Juvenile Rheumatoid Arthritis, who may be struggling very hard to learn to walk or to maintain existing physical functioning. She has been exploring the usefulness of working with the children in informal groups, often converting the natural grouping of youngsters she finds on the Unit into play interview situations. Useful though all these efforts have been, they do not substitute for the kind of children's group work program the Section formerly offered. The individual caseworkers cannot provide the daily contacts, the recreational program nor all of the therapeutic benefits that such a program afforded.

One of the most gratifying developments on this Section, in this period, has been workers' involvement in research activity. In May, Mrs. Turk completed a paper "The Impact of Family Functioning of the Child with Cystic Fibrosis." This paper is scheduled for publication in Pediatrics in the near future. Her work on this piece of research enriched her practice activities on the Service in several ways. This indication of her especial interest in the Service paved the way for an increase in the number of referrals from medical staff. The families of patients responded to the concern for their problems this inquiry showed and, in many instances, areas of discomfort and anxiety were opened up for further sharing and working through in casework contacts. One of the principal findings of this paper was that many of these families find themselves caught in a web of silence which prevents them from talking over problems together and from dealing with reasonable openness and directness with the Cystic Fibrosis child himself and his siblings. This finding highlighted the importance of undertaking medical planning, not with just one parent but with both, taking the total family into consideration.

Mrs. Weissman's paper entitled "The Social Worker as Part of a Metabolic Research Team" was also completed in May and has been accepted by the Journal of Chronic Diseases. In this paper, Mrs. Weissman reflects on the kind of preventive and supportive casework activity which aids the adjustment of patients to the confining and demanding metabolic regimen. Mrs. Weissman has utilized much of this material in orienting social workers and dietitians from clinical research units at other university hospitals to the function of social work on such a unit. Most recently, she attended a workshop at the University of Alabama for an exchange of experience and information with other social workers from comparable units.

NIAID Social Work Section

During this period there have been a considerable number of long-term patients on this Institute. Certain patients, either adults or children, may stay at the Clinical Center for as long as 18 months. For most of these patients the periods of acute illness are fortunately intermittent; most of the time they feel quite well, are fully ambulatory and able to take part in the activities of the hospital. Therefore, in the casework emphasis on this unit, the milieu aspects have come into increased prominence. We have been particularly aware of the importance of using this setting to further educational or vocational goals.

The Mexican Leprosy patients have also been interested in becoming more vocationally qualified as they have become a part of the life in this North American world. They desire to learn English, to improve their primitive Spanish and to better equip themselves vocationally. In relation to all of these patients, there is a concomitant investment in providing the kind of discharge planning which will continue to help them to secure a better vocational adjustment within the limitations of their illness.

In line with the presenting problems on this Institute, Mr. Gallagher has been interested in studying the effect of long-term hospitalization on the social values and social functioning of patients coming from lower socio-economic brackets. Mr. Gallagher's tentative hypothesis is that hospitalization may be a constructive and educational experience with useful carry-over into certain areas of the patient's life and functioning.

NIMH Social Work Section

The Social Work Program on the NIMH continues to focus on the family, directed towards an understanding of the psychosocial dynamics of family life. Gradually the projects are extending more into the communities to study family units first hand. This is in line with developing trends in the mental health field.

Since the General Psychiatric Service under Dr. Gentry Harris was discontinued, Mrs. Yolande Davenport devotes her time chiefly to recruiting patients for the various projects on NIMH and to the Familial Dysautonomia Study. By centralizing recruitment for the several projects under one Intake Social Worker, many of the confusions and dissatisfactions that existed among potential sources of referral have been eliminated, resulting in more appropriate referrals, quicker action, and better referrals back to the proper community agencies when applicants do not meet the criteria for an NIMH study.

In the Familial Dysautonomia Project, Mrs. Davenport is studying the psychosocial aspects of the illness, interpreting the dynamics of patients and families, and this is incorporated into the research findings for a more comprehensive study. She is developing an independent social work research study dealing with modes of adaptation of parents to a chronic illness.

Mrs. Carmen Cabrera continues on the "Difficulties in Growth and Adaptation in Adolescent Personality Development" (College Breakdown) Project. The material related to formulation and analysis of family development has been almost entirely her responsibility from the outset and at present she is preparing analytical summaries of her cases to be used as family profiles in the study of identity patterns of behavior and identity problems detected in the adolescent patients under study. This is in addition to her participation as co-therapist in all the family therapy sessions with the patient's therapist.

Miss Carol Hoover is performing essentially the same functions on the "Family Relations in Schizophrenia" Project as last reported. Her paper "The Embroiled Family; A Blueprint for Schizophrenia" is completed except for editing. Based on her experiences over several years with many such families, it stresses the attempts at closeness of family members to the

sick individual and the lack of health opportunities to develop closeness.

Mrs. Toby Oberdorfer, Social Worker on the Multi-Dimensional Study on Psychoses, is currently concentrating her efforts on the follow-up of a sample of the patients discharged from the Unit. She visits the homes of patients and interviews the families and employers while a psychiatrist and psychologist interview the patient. The interviews of each are compared for discrepancies and evaluated.

The three social workers on the Child Research Project, Messrs.Paul Blank, Walter Sceery and Robert Mahon, study average "normal" families living in the community, gathering psychological and social data in young married couples, young parents and in very young children, recognizing and defining problems in the "normal" which may or actually do develop into emotional illness. As the couples move from a dyadic to a triadic family, additional problems may develop requiring individual or group psychotherapy. Thus, the social workers draw on their clinical skills as well as functioning in a research capacity.

While the study of monozygotic twins discordant for schizophrenia is well underway, we regret to report that we have not as yet been able to recruit a social worker for this position. Partly, this is due to the unusual requirements for the position and, in no small measure, to the fact that we have not been able to recruit at a salary which is competitive for positions at the advanced caseworker level. Here again we look forward to the reclassification of the Clinical Social Work Series as a remedial measure.

The book on The Genain Quadruplets, A Study of Heredity and Environment, came off the press and received several complimentary reviews from newspapers and publications. Mr. Stanley I. Hirsch, Chief of the Mental Health Social Work Section, wrote the chapter on the father, and Mrs. Betty Basamania and Mrs. Blanche Ellis, former Clinical Social Workers on the NIMH Social Work Section, wrote chapters on the mother and community, respectively.

Another publication of note was Human Aging in which Mr. Paul Blank collaborated with Dr. Marian R. Yarrow, Dr. Olive W. Quinn and others in the Chapter on "Social Psychological Characteristics of Old Age."

Mrs. Charlotte Wilkie's "A Study of Distortions in Recording Interviews," was published in Social Work.

NINDB Social Work Section

The primary focus of the Social Work Program on NINDB has been on the maintenance of effective casework services to patients despite severe and prolonged staff shortages. The medical programming on Medical Neurology and Opthalmology has remained about the same. On Surgical Nuerology, there have been gradual shifts in the patients population as the number of Temporal Lobe patients were reduced and there was a gradual increase in patients with involuntary movements, brain tumors and head injuries. In addition, Pediatric Neurology now has six beds rather than the two it formerly had. The needs of

all of these patients are numerous, and because there is a lack of facilities for their care, social work planning is very extensive and time consuming.

A cooperative project of NIMH and NINDB was set up on 4-West. NINDB undertook medical supervision and, as part of patient care, responsibility for social work coverage. These patients were all well-known to the surgical neurology social worker from previous admissions. Almost all required some social work assistance during their stay in adjusting to this different kind of hospitalization, a different ward, new personnel, and in discharge planning. It is anticipated that this project will be repeated.

The research project "A Follow-Up Study on Changes in Social Functioning After Surgery for Temporal Lobe Epilepsy" was completed by Mr. Robert Savard and Miss Evelyn Walker. At the request of the Clinical Director, Mr. Savard and Miss Walker prepared a condensation of this paper; this condensation became one section of an address presented by Dr. Ayoub Ommaya in London, June 1963. More recently, it has been accepted for publication by Social Work.

During the staff shortages, it has been possible for the Social Work Staff to maintain full coverage on both the Medical and Surgical Services, but it had become necessary to limit service to Opthalmology patients to that requested specifically by staff or patient. The rise and fall of the caseload on this Unit during the year, dramatically tied in with the continued presence or absence of a worker, visible to patients on the ward and available to medical and nursing staff for consultation.

Among the social work research projects or studies in the continuation phase were: the NINDB Staff Project on Interruption, for which Mr. Polcari took editorial responsibility, and the Study of Loneliness in which Mrs. Scherp and Mr. Roatch were collaborating moved into the writing stage.

In summary, each Institute's activity reflects an adaptation of social work skills and techniques not only to a challenging range of problems but to a changing range of problems dependent upon shifts in research protocols, thus requiring a flexible and creative response on the part of the social work practitioner to the needs of changing patient groups.

PATIENT WELFARE FUND

The Patient Welfare Fund continues to maintain a minimal balance of income over expenditure (See Tables 1 & 2). Certain measures were taken in Fiscal Year '63 to control expenditures in special programs and in the most costly category, Family Maintenance (See Tables 3 & 4).

While it has been possible to place a workable ceiling on expenditures in special programs, that is, the normal prisoner volunteers and the children's activities, it has not been possible to put a workable ceiling on Family Maintenance. The following three factors make it very difficult to control expenditures in Family Maintenance: First, the cyclical nature of the children's illness results in having a number of child leukemia patients seriously ill at the same time, necessitating a substantial outlay of funds

without regard to budget ceiling. The consequence is that the samll capital in the fund is rapidly diminished. The second factor is that the number of beds for children and adolescents with leukemia was increased by eleven in the first quarter of Fiscal Year '64. The third factor is that the length of the treatment period has increased from two and one-half months to five months.

During this reporting period, additional efforts have been made to increase income. Foremost among these was the utilization of the NIH Record to inform the NIH Staff of the purpose and needs of the Patient Welfare Fund. During the past year, three interesting and informative articles have been written in the Record. The response has been heartening. Staff members have contributed honoraria and some staff donated to the Patient Welfare Fund in place of an exchange of Christmas greeting cards. There have also been a number of contributions from the patients and their families in gratitude for the services rendered to them. These are all most welcome; nevertheless, our income continues to be 60% from Recreation and Welfare Association and 40% from other sources, totaling about $13,000 per year, always perilously close to our rate of expenditure (See Tables 5, 6, 7).

In January, 1964, the Chief of the Department was asked to chair the Patient Welfare Committee for the Recreation and Welfare Association and is now in the process of reporting to them on the status and needs of the Fund.

Generally, we are concerned that over 50% of total expenditure is directed toward one problem area, thus limiting the availability and flexibility of the funds for other patient needs. The urgency of the problem on Children's Leukemia is not likely to abate for some time. The facility mentioned previously in the report seems to hold the most likelihood for meeting the problem of the family members who need to be here because of the patient's serious illness and who are in acute financial distress. It also frees the fund for more flexible utilization across Institute programs.

RECRUITMENT

Since July 1963, we have recruited eight social workers. This required a considerable investment of total staff, particularly administrative staff, in the effort to interpret program objectives to numerous applicants. We did, however, achieve the goal of filling the vacancies and did so with social work practitioners with excellent backgrounds at various levels of experience.

Mrs. Myrna Cobbledick reported for duty on December 16, 1963, and was assigned as the social worker to cover 2-East, NCI. Mrs. Cobbledick is a graduate of the Denver University School of Social Work and was previously employed at the University of Colorado Medical Center.

Miss Barbara Feroe reported for duty on the NCI Social Work Section and was assigned to 12-West for work with the Solid Tumor and Chemotherapy patients under the supervision of Mrs. Belvin Blandford in accordance with the Department's new policy of affording supervisory experience to advanced

clinical social workers. Miss Feroe is a graduate of the School of Social Work at the University of North Carolina. Her field work assignment was at the Spring Grove State Hospital.

Mrs. Ellen Lee, a 1963 graduate of Carol Woerishoeffer Graduate Department of Social Work and Social Research of Bryn Mawr College, was recruited for a position on the NHI Cardiology Unit. Mrs. Lee had her most recent field work assignment in the Child Psychology Clinic of St. Christopher's Hospital.

Mrs. Melitta Leff, a graduate of the Smith College School of Social Work, was assigned to NIMH as a part-time worker. She previously worked as a caseworker at Family Service in Cincinnati, and was most recently employed at the Community Psychiatric Clinic in Bethesda, Maryland.

Mrs. Rebecca Griffin, a graduate of Howard University, was assigned to Medical Neurology, NINDB. She was formerly employed in the Cancer Home Care Program at Georgetown University Hospital, the Child Guidance Division, D.C. Bureau of Mental Health, and most recently as a family counselor with the Relocation and Management Division of the Redevelopment Land Agency.

Miss Karen Schulman was graduated from the University of Chicago School of Social Services Administration in June 1963. Her second year field placement was at the University of Chicago Clinics and Hospitals. She was assigned to NHI.

Miss Barbara Spillman was graduated from the Columbia University School of Social Work in June 1963. Her most recent field placement was at the Roosevelt Hospital in a combined medical and psychiatric unit. Prior to entering graduate school, Miss Spillman was employed as a Child Welfare Worker in Portland, Oregon. She was assigned to NIAMD.

Mrs. Elizabeth Schumann, a part-time worker, was assigned to the Eye Service. Recently, she has devoted her time exclusively to her home; however, previously she was employed as caseworker and a supervisor by the Family Service Bureau, United Charities of Chicago, and as a training supervisor for the University of California at Los Angeles by the Los Angeles County Bureau of Public Assistance.

STAFF DEVELOPMENT

In order to meet a variety of informational and developmental needs among staff, several new programs have been introduced.

In the Annual Program Review, staff members identified a need for greater knowledge of studies and particular areas of interest being developed in other Institute Social Work Sections. As a result, monthly Interchange Meeting was established. Since February 1962, twelve presentations were made ranging from practice techniques to studies in progress. Ten different staff members presented material.

Social Work Services to the Hospitalized Child was the subject of a two-day seminar led by Mrs. Emma Plank, Director of Child Life and Education, Cleveland Metropolitan General Hospital, and Assistant Professor of Child Development at the School of Medicine, Western Reserve University. This seminar was organized in response to the concern of many staff members about the fact that child patients are in the minority on the majority of nursing units. Therefore, there is less opportunity to develop expertness in work with children as contrasted to the greater experience which can be gained in working with adults. Mrs. Plank, a recognized authority in this field, was able to give many specific suggestions for meeting the needs of child patients in order to diminish reactions to illness, treatment procedures and separation from home.

Casework workshops for staff members recently graduated from Schools of Social Work have continued. This program is focused on supplementing the individual supervision received and, through group interchange, to facilitate the integration of social work theory and concepts in daily practice. Miss Barbara Murphy led eight sessions on problems of differential diagnosis. Mr. Lawrence Burke led eight sessions on the relationship between theory and casework treatment of patients in the current caseload.

A series of four orientation sessions on research within the Department was added to the orientation program for new staff members. These were led by the Chief and the Assistant Chief. They were designed to clarify the Department's view of the relationship between practice and research, and the Department's expectation of staff participation in research. By introducing this facet of Department function in a more formal way at this early point, it is anticipated that new staff, while concentrating primarily on their service function, will at the same time begin to identify ideas for further study.

The staff development programs related to increasing research competence, previously conducted by visiting consultants, now are planned and provided by Dr. Geraldine Conner, Staff Research Consultant.

The yearly review of program by total staff, begun in Fiscal Year '62, was continued. Again fruitful suggestions were made for improving various areas of Department operations.

During the coming year, the staff will carry forward the discussion of the care of children and adolescents in hospitals under the leadership of Selma Fraiberg. Planning for the total staff development program for Fiscal Year '65 will be done in consultation with representative staff members in order to insure its applicability for the various levels of staff experience and interest.

PROGRAM DEVELOPMENTS

RESEARCH CONSULTATION

The Research Consultation Program was formally initiated in January, 1963, by Dr. Geraldine Conner. As this particular program is in its infancy, the

emphasis is upon helping the social work practitioner formulate ideas derived from daily practice into a small study or a series of studies, individual or interdisciplinary, which will make it possible for him to transmit reliable and valid observations about some aspect of social functioning in chronic disease to the Public Health field.

During this time period, consultation has been given on 27 projects, involving 29 individuals. The current status of the group of projects is:

Completed	11
Not Completed, Active	5
Not Completed, Inactive	7
Abortive	4
TOTAL	27

Two of the completed projects were administrative and reports were prepared and presented for intra-department use.

The rate of publication for the Department between 1955 and 1962 averaged two per year. During this past year, five projects on which Dr. Conner gave consultation have been published or accepted for publication. Another has been submitted. The soundness of the content and relatedness to the field of chronic diseases is evidenced by the fact that three of these papers were accepted by medical journals -- Pediatrics, Public Health Reports, and Chronic Diseases.

STATISTICS

The Department is in the process of trying out a new system which will more adequately reflect the range in quantity and quality of social work services. Our previous system was based primarily on a case unit without regard to the number of individuals to whom service was given. We are now attempting to refine a system which will consider not only the case unit, but also includes a client unit. This will make it possible to identify the number of individuals served and types of problems involved.

The new system, begun in January 1964, is hand talleyed and enables each Institute Section to report independently. In addition to the case and interview count captured by previous method of reporting, the new method makes it possible to secure the following additional data:

1. The actual number of persons (clients) who receive social work services within a case. This includes individual family members as well as patients.

2. The incidence of principal problems of individuals seen within each case. (Three months experience indicates that these categories give a range and richness of description of principal problems not previously available. Also, concentrations of particular problems among patient groups will allow

a base from which to judge the particular skills needed by the assigned worker.)

3. Assess the numbers of persons seen and numbers of interviews held with persons who are in the screening stage prior to acceptance for inclusion in NIH projects or who need help in solving problems preventing admission after being accepted for a project.

Client's Principal Problem

The frequency of problem occurrence is illustrated in Table 8. In reality, the six problem types represent two general categories: (1) problems which have their origin in the illness, and (2) problems which have their origin within the adaptive capacity of the individual. The Table shows that 58% of the principal problems were of the first kind where service was needed in the areas of reaction to illness, hospitalization, and need of resources. In contrast, 42% of the principal problems were of the second kind; problems in family relationships, separation, and readjustment in living patterns.

It is interesting to note that the most frequent problem for which service is given on NCI is reaction to illness reflecting the threat cancer poses; whereas on NHI, the most frequent problem relates to hospital experience, reflecting primarily the many problems attendant to facing cardiac surgery.

The need for resources -- economic, equipment, treatment, etc., is the next most frequent need and is centered in NCI and NINDB patients. Problems in family relationships come next, centered in NCI, NIMH, and NINDB, reflecting the frequency with which physical as well as mental illness disrupts family equilibrium. The need to reorder and change normal living habits when chronic illness is present is fifth in order of frequency, while overwhelming loneliness due to separation from home is the sixth.

It should be noted that no problem listed can be considered infrequent. Since staff were required to designate one principal problem per individual to whom direct casework services were given, this chart does not reflect the fact that, in reality, patients and family members face multiple problems falling in more than one of these categories and are assisted with them by the caseworker.

While no statistics are available concerning the association between length of patient stay and principal problem, what is known about the casework process makes it reasonable to assume that the split between illness and adaptive problems reflects the necessity to assist with the problem uppermost in the patient's mind before the deeper problems can become manifest. Thus it is probable that problems of the second type are most apt to emerge from long-term or readmitted patients.

Ratio of Cases to Clients

In the previous reporting system, patient count only was reported. This did not reflect the actual number of persons served - here referred to as clients.

In illness, family members not only face the same problems as are faced by the patient, but also face problems of their own which, if unresolved, can add to the burden already being carried by the patient. Our records show that 1,907 clients were involved in 1,380 cases. Since there is always a patient involved in each case, in addition to the 1,380 patients served, 527 family members were served during the three-month period. There were 1.37 cleints per case.

In-Patient Coverage

Defining and measuring the extent of coverage presents a very complicated problem considering the facets of program it is attempting to assess: in-patient service, out-patient service, screening and pre-admission service. The Department is presently working on a system to more accurately assess coverage rate. At the present time, on the basis of a sampling of workload, there is evidence that the in-patient coverage ranges from 80% to 100%.

Out-Patient Coverage

The patients seen on an out-patient basis fall into two categories. Those served who are under active study and those served to determine if they are suitable for study or who need help to come under study. The following Table shows the number of patierts in follow-up status who were given service in the third quarter of Fiscal Year '63 and in the third quarter of Fiscal Year '64.

	1963	1964
January	50	56
February	50	59
March	53	90
TOTAL	153	205

It can be readily seen that there was an increase of patients in follow-up status receiving social work services in 1964.

In addition to the 205 out-patients, 61 patients were seen for screening to determine the likelihood of their ability to fit into a project; or for assistance to enable them to become patients after they had been accepted into a project. Comparable data were not available for Fiscal Year '63.

Interview Count

Tables 9 and 10 summarize volume of interviews conducted with or on behalf of patients. Because of unavailability of data for some months, totals for the year have been estimated from the average number of interviews held during the months in which data were available. Comparing the estimates

for Fiscal Years '62, '63 and '64 yields the following:

Fiscal Year	No. of Interviews
1962	40,400
1963	39,642
1964	44,000

Increased staff in Fiscal Year '62 resulted in an estimated increase of 5,000 interviews over 1961. In 1963, staff shortages stemming from resignations resulted in a slight drop in interviews. Staff additions during the first two quarters of Fiscal Year '64 resulted in an estimated increase of about 4,500 interviews over Fiscal Year '63.

By comparing the number of persons served in the third quarter of 1963 with the number of interviews held during the same period, we estimated that each person served (patients and family members) involves a minimum average of six interviews.

Related Activities

In addition to direct services to patients, staff is involved in a variety of activities which are necessary for maintaining social work services at a high level of quality and integration into the total plan for research and medical care. These include attendance at ward rounds and conferences to maintain adequate communication, research, administrative and staff development activities within the Department, and activities within the professional community.

Tables 11 and 12 give a breakdown of the amount of time spent in these activities together with the percent of the total amount of time so spent in each. From this data we estimate that staff spends about 30% of total available time in activities supporting direct social work services.

Worksheet

In order to facilitate the early arrival of the social worker's recording on the chart, the Department reinstituted the use of the worksheet. The worksheet is used to record the following kinds of information:

1. Important items of information which must be available in the chart before the typed record can be prepared.

2. Items which will probably have no permanent value but are of temporary use.

Assignment of a Gray Lady to the Social Work Department

After discussion with Mrs. Blandi, Chairman of the Clinical Center Gray Service, and further discussion with Dr. Himmelsbach, it was agreed that we would experiment with the idea of having a Gray Lady assigned to the Social Work Department one day a week to work under the direction of Mrs.

Lucia Mason, NIAMD. While Mrs. Donelan, the Gray Lady assigned, is a professional social worker, her primary function would not be professional social work but rather friendly visiting. It was hoped that the experiment would provide some guidelines for the performance and utilization of friendly visiting on various units.

Experience indicates that friendly visiting by one consistent person has been particularly helpful to patients separated from their families or isolated by the nature of their disease. Guidelines for further development of the program are being worked out between the Gray Service and the Social Work Department.

PROBLEM AREAS

1. Threaded throughout the reports from Social Work Section Chiefs was the need for additional psychiatric consultation, both to the unit and to the caseworker. All of the Institutes have within their patient census a number of seriously disturbed people. Since NIMH can only give consultation, a great deal of the responsibility devolves upon the social worker. We believe it is important to consider more continuity in psychiatric consultation and the possibility of having psychiatric care more directly available to patients on the medical units.

2. As noted earlier in the report, there is a real need at this time for a facility for the parents and relatives of seriously ill patients.

3. The Mexican patients need to learn English and would profit by some improvement in their Spanish. Up until now, the English lessons have been given on a volunteer basis and thus far it has not been possible to follow through with consistency. There is a need to recruit either a different kind of volunteer or to pay a tutor for the lessons.

4. During the year, five of the Social Work Sections have moved into different office space. Generally, we are well located. The one problem area we envision is in having the social worker on the 12-West Unit and the social worker on the 13-West Unit located on 1B. The problem here is that neither of these groups of patients is able to travel any distance for private office interviews. We believe this will need to be carefully watched.

5. While we have a competent and devoted secretarial staff, we are faced with continual problems in turn-over and in re-training because the classification for these positions is not competitive with other comparable positions within the Institutes. We look forward to the Desk Audit and toward the possibility of reclassification.

PROGRESS

1. The addition of a number of young workers has been thought-provoking and stimulating for the total staff. Professionally they have contributed a great deal and they have been instrumental in helping the more advanced

caseworkers to explicate some of their principles of action for the utilization of the new professional worker.

2. The addition of a full-time research consultant to the staff has enriched and rounded out the staff development program, and led to publications of consequence for the field of Public Health.

3. As noted before, the review of the Clinical Social Work Series has been most helpful in so far as we can anticipate a journeyman position at a GS-11 and the addition of a social work assistant. We are equally pleased that there is a possibility of establishing advanced positions in group work, research and community organization in relation to those already described in the Classification Standard.

4. The opportunity afforded to a number of our staff to attend professional meetings was an excellent one. This is especially important now that we have a number of staff who are presenting papers, and also for younger staff members who need to learn more about the breadth of their own profession through attendance at such meetings.

5. While the revision of the statistical system is very new, we believe that it will enlarge our knowledge of the needs of patients and appropriate social work services to meet those needs.

6. During the past year, we have clarified the function of the chief secretary in the office, and she has willingly and ably taken over many of the administrative tasks which have become necessary in this position.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Lonely Sinner

Principal Investigator: Carmen Amoros-Cabrera

Other Investigators: None

Cooperating Units: Study on: "Difficulties in Growth and Adaptation in Adolescent Personality Development."

Man Years: (27 months)
Total: 108 hours
Professional: 108 hours
Other: None

Project Description: In the 22 families out of the total project sample, the investigator participated in family therapy and had regularly scheduled interviews with the parents.

Through contacts with the adolescent patient and the family, the following formulation was developed: (1) That these relatively well educated, sophisticated parents may have exaggerated the concept of fostering independence in the child; may have intellectualized their feelings of rejection; and may have thus created an atmosphere of extreme loneliness, where the messages conveyed by the child in an effort to ask for limits, and for parental intervention, in the painful task of channeling impulses, may have been ignored. As a consequence such children presented problems that were consistently rationalized with the support of theoretical knowledge. Such problems gradually increased without success in obtaining the much needed involvement with the parents until extreme frustration may have induced extreme personality disorganization.

Method: Twenty-two cases were examined but one case was selected to exemplify this concept. The examination of the material obtained from family sessions, and sessions with the parents was based on isolation of events and interactions, communication, etc., that seem to spell out the stated formulation.

Findings: Classification of the evidence obtained from the material examined is now in process.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: After Hours Calls for Social Work Services

Principal Investigator: Belvin R. Blandford

Other Investigators: None

Cooperative Units: None

Man Years (January 1, 1963 through June 30, 1964)
Total: 130 hours
Professional: 130 hours
Other: None

Project Description:

Objective: The purpose of this study was to determine the number of unscheduled after hours calls received by the professional staff of the Social Work Department, the problems these calls involved, the time required, and whether the request for service were similar or dissimilar to those received during usual working hours.

Methods Employed: From June 1963 through February 1964 the social workers in the Clinical Center were asked to complete a questionnaire on the next working day after an unscheduled call was received.

Major Findings: During the nine months period forty-nine unscheduled calls were received. Workers in the Heart Institute received twenty-three calls and those on the Cancer Institute sixteen calls. The remaining calls were divided about equally among the other institutes. Forty-two of the forty-nine patients involved had been previously known to the worker.

The time involved with these calls ranged from less than fifteen minutes to seven hours. Eleven times the worker returned to the Clinical Center. The majority of the problems could be handled by phone. Action on a request was delayed in only five instances.

Seven cases were unlike the kind of request ordinarily received during working hours. They involved situations for which no one seemed to have assigned responsibility or situations which could occur only after normal working hours.

The majority (42) of the calls involved situations in the range of problems

usually handled by a social worker; thirty-three required immediate action, the rest were of a continuing nature. Most frequently the call came because of a family crisis brought about by the death of a patient or because of an environmental need of the patient or of his family.

Part B Included: No.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Does Surgical Success in Children with Heart Disease in the Latent and Adolescent Group Result in Significant Positive Changes in Social Functioning?

Principal Investigators: Vincenza Bowles
Barbara A. Murphy

Cooperating Units: None

Man Years (Fiscal Year 1963-1964)
Total: 300 hours
Professional: 300 hours
Other: None

Project Description:

Objectives: The purpose of this study is to learn whether children who have been physically improved by cardiac surgery experience concomitant changes in social functioning as measured by their ability to perform age-appropriate tasks before and after surgery.

The project will study the functioning of two groups of children, those in latency period (6-10 years) and those in the adolescent period (16-21 years) admitted to the Clinical Center of the NIH Heart Institute. The children will have been judged symptomatic prior to surgery, and physically improved following surgery by the physician.

Methods Employed: The developmental theories of Freud, Erikson, Josselyn, and others have been used as a basic frame of reference for determining the significant life tasks of childhood. The theoretical developmental tasks have been translated into a series of perceivable behaviors. From these a schedule has been devised which will contain a series of questions concerning life tasks as they relate to latency and adolescence.

The children will be used as the primary source of data. The schedule will be administered in an interview situation at two different points in time: before surgery and following a medically appropriate period after surgery. In order not to lose information on the children in the specified age groups who were previously operated on within the last year, the schedule will be administered to them as they return to the Clinical Center for follow-up, with an attempt to obtain retrospective data on their functioning prior to

surgery. While the postsurgical responses of both groups are comparable, it may or may not be possible to utilize the retrospective material.

Present Status of Project: Part of the schedule has been devised and is in process of being pretested with both well and ill children between the ages of 6 and 10.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Tag Team Interviewing of Parents with Leukemia Children

Principal Investigators: Lawrence Burke
Joel Vernick

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1963)
Total: 50 hours
Professional: 50 hours
Other: None

Project Description:

Objective: Experience with parents of leukemic children suggested that joint interviewing with both the parents and child involved provides greater uniformity and consistency in communication, thereby reducing discrepancies and possible distortions in the handling of the maternal parental concern for maximum care for their ill children.

Significance: Technique hopes to penetrate deeper into the true feelings, thinking and attitudes of parent at a faster pace than the traditional interview. Reassurance, and support, when needed, is doubled in its effectiveness.

Method: Interviews are process recorded immediately after they take place. When sufficient interviews are available they will be evaluated for depth of content, frankness of feelings expressed within a given time span.

Part B Included: No

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Study of Social Work Services for Research Patients on a Cancer Ward.

Principal Investigator: Rintha M. Carter

Other Investigators: Kathryn K. Himmelsbach, Program Supervisor, NCI, SWS
Geraldine Conner, D.S.W., Social Work Research Consultant

Cooperating Units: None

Man Years (calendar year 1963)
Total: 60 hours
Professional: 60 hours
Other: None

Project Description:

Objective: The purpose of this study was to determine first, the kinds of services needed, and second, who observed the needs of these services. A third question emerged during the study as to whether differential were found in the patients and their needs in the single--as opposed to the multiple--referral group.

Methods employed: All referrals to the social worker were categorized in accordance with the nature of the social work requested and the sources of referral on the surgical unit of National Cancer Institute over a six-month period.

Major findings: The patients on the surgical unit of National Cancer Institute tended to have significantly more referrals from the patient group and the major reason for referral was for medical casework. Though the phenomenon of the single and the multiple referral groups was observed, no reason was found to account for the multiple referrals of some patients as opposed to other.

Proposed Course of Project: In stage of editing.

Part B Included: No

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: A Study of Modes of Adaptation to Chronic Illness by Parents of Children With Familial Dysautonomia

Principal Investigator: Yolande B. Davenport

Other Investigators: None

Cooperating Units: NIMH Project: Disposition and Metabolism of Catecholomine Hormones in Familial Dysautonomia

Man Years: (Calendar year 1963)
Total: 60 hours
Professional: 60 hours
Other: None

Project Description: Familial Dysautonomia is a genetically determined life threatening illness occurring in children which affects the autonomic nervous system. The emotional instability of many of these children, essentially the result of a basic physiological dysfunction, results in disturbed behavior which has profound and often catastrophic effects upon family functioning. Emphasis in the research will be upon the psychosocial aspects of the illness with the intent of studying behavorial management techniques conducive to optimal adjustment.

Methods Employed: A self administered questionnaire designed to elicit information regarding variances in adjustment as well as differences in parental attitudes and reactions was mailed to parents of children whose names appear on a list of the known cases of Familial Dysautonomia in this country.

In addition, approximately 10 child-parent pairs admitted to the Clinical Center to participate in biological research studies will be interviewed in order to secure comprehensive social histories. Data regarding parent-child interaction will be systematically collected from observations charted on the ward by nursing staff, and psychological testing of children and parents, both projective and intelligence, will provide an additional method of assessing the relative degree of adjustment and disturbance in the groups.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Effect of Long Term Hospitalization at the National Institutes of Health on the Attitudes and Values of Patients of Poor Economic and Social Backgrounds.

Principal Investigator: Thomas G. Gallagher

Other Investigators: Dr. Geraldine Conner
Mrs. Lucia N. Mason

Cooperating Units: None

Man Years: (calendar year 1963)
Total: 35 hours
Professional: 35 hours
Other: None

Project Description:

This project, which is still in the planning stages, will evaluate what changes, if any, occur in the attitudes and values of patients who come to NIH from poor social and economic backgrounds and remain here for a period of at least six months. We are interested in finding out if there are any changes in such things as the patient's living standards, behavior, family role, future goals, etc., and whether these changes are permanent or temporary. If the specific causes of these changes can also be determined, it will help the staff to realize what areas are most meaningful to patients so that more of the staff's attention can be focused there.

This study will show the effect that an environment like the Clinical Center has on long-term patients and may in this way be useful in helping to show the benefits of environment manipulation on people in situations other than a hospital setting.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Embroiled Family: (An etiological study of schizophrenia development in a family type of described relationships and qualities.)

Principal Investigator: Carol Hoover

Other Investigators: None

Cooperating Units: Family Studies Section, APB

Man Years: Calendar Year 1963
Total: 100 hours
Professional: 100 hours
Other: 25 hours

Project Description:

Objectives: (1) To describe a variety of family in which schizophrenia frequently occurs. (2) To formulate etiological hypotheses consistent with this occurrence.

Methods Employed: Analysis of interview and historical record material of families seen as part of the Family Studies Program, correlated with previous diagnostic, history getting, and therapeutic experience of the investigator.

Major Findings: In an embroiled family, the child who responds to high parental demands for strength and closeness, without feeling his parents genuinely close or his own strength great enough for the task, may eventually become schizophrenic.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Perception of roles, closeness patterns, and capacities by members of families in normal and other categories.

Principal Investigator: Carol Hoover

Other Investigators: This project is closely allied with "Patterns of Family Interaction: The Family Rorschach Study of Normal Families", of which the principal investigator is Nathen Loveland. Other investigators on that project include Lyman Wynne, Margaret Thaler Singer, Yolande Davenport, Gary Morris and Carol Hoover.

Cooperating Units: Family Rorschach Study (see above)

Man Years (Calendar year 1963)
Total: 200 hours
Professional: 80 hours
Other: 120 hours (transcribing taped interviews)

Project Description:

Objectives: To evaluate: (1) Possible differences in acknowledged roles, closeness, and expectations of one another, in normal families as compared to families containing at least one neurotic or schizophrenic member (2) Any variation between families of these diagnostic categories in the degree of explicit awareness or ability to present clearly the different perceptions; (3) Comparative impressions by the investigator of unacknowledged social relationships and mutual expectations within families of these types based on clinical observation and history material; and (4) Degree of sibling variation in functioning within families of the different categories.

Methods Employed:

1. An interview with both parents, during which they are asked questions about themselves and all members of the immediate family group regardless of age.

2. A brief interview with each of the two oldest siblings, during which the same questions, where applicable, are asked of them.

3. These interviews are supplemented with (a) history material obtained,

not directly from the families, in the course of my participation in the Family Rorschach project, plus (b) in most cases, observation of the joint Family Rorschach interviews.

4. Each parent is asked to prepare a Social History Form R, (In standard use on The Family Studies in Schizophrenia and the College Projects,) to facilitate possible more limited comparisons with families on these projects at some future date. In addition, parents are asked to assess the health of each of their children on a separate but similar form.

5. Summary evaluation of each family is prepared after a careful review of transcribed interviews and other material to form the basis for further study.

Major Findings: None as yet.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Relation Between Precipitating Factors of Depression and Psycho-social Background

Principal Investigators: Melitta Leff
Dr. William Bunney

Other Investigators: None

Cooperating Units: Depression Study, NIMH

Man Years: (Calendar Years 1963)
Total: 100 hours
Professional: 100 hours
Other: None

Project Description:

Objectives: This study concerns itself with the meaning of precipitating factors in a depressive episode.

What are recurrent precipitating factors in the group of patients studied? Are some of the factors observed more significant, as judged by their frequent occurrence? Is there a pattern in the multiplicity of factors? And, most important, can one identify and correlate a patient's sensitivity to given precipitating factors on the basis of his early background?

Methods Employed: Complete records of all patients on the project are being analyzed for:

(1) Childhood background -- including parental loss, identify problems, relationship difficulties.
(2) Previous depressive episodes, if applicable.
(3) Precipitating factors in depressive episode leading to hospitalization on this project.

Major Findings: The data is in the process of being collected and categorized. It will have to be analyzed with a view to testing out hypotheses regarding association of precipitating factors to patients' background experiences.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: A Study of Predeterminants of Personality

Principal Investigator: Robert Mahon

Other Investigators: None

Cooperating Units: Nursery School project - Child Research Branch, NIMH

Man Years: (Calendar Year 1963)

Total: 60 hours
Professional: 60 hours
Other: None

Project Description:

Observations of behavior of Nursery school children and interviews with their mothers to develop hypotheses concerning individual difference in the areas of needs and activity levels.

Findings: A theoretical paper will be written presenting a conceptual scheme for understanding some of the factors which contribute to individual personality development. This will be based on observation and interviews with over 100 mothers and their children. Children would be identified as falling along a continuum in the two areas studied and this would seem to have significance in influencing their perception of the environment as well as contributing to the parents' response to them.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH

Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Reactions of Patients Hospitalized on an Infectious Disease Service to the Experience of Isolation

Principal Investigator: Lucia N. Mason

Other Investigators: None

Cooperating Units: None

Man Years: (Calendar Year 1963)

Total: 120 hours
Professional: 100 hours
Other: 20 hours

Project Description:

Objectives: This project is intended to provide both descriptive and subjective material on isolation as patients experience it, and to test certain hypotheses about factors enhancing or disrupting patient's emotional adjustment to isolation.

Data have now been gathered from patient respondents on the NIAID and are being processed. Findings are not yet ready.

Method: A questionnaire, a series of structured interviews on the hour-by-hour experience of being in isolation as well as a final unstructured report by the patient on the various possible emotional impacts of isolation are the data gathering devices used in this study. Material has been gathered from several respondents, and their adjustment to the isolation experience rated by the use of scales for use in the predictive section of the study. Unstructured interviews with a number of additional patients will serve as a basis for the descriptive portion of this study.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: An Evaluation of the Effectiveness of a Staff Educational Program Designed to Increase Worker Competence.

Principal Investigators: Barbara A. Murphy

Other Investigators: None

Cooperating Units: None

Man Years: (Fiscal Year 1962-1964)
Total: 64 hours
Professional: 64 hours
Other: None

Project Description:

Objectives: To develop and test an instrument with which to assess the effectiveness of staff education programs which are focused on increasing specific areas of competence in the inexperienced professional caseworker. An evaluation of the effectiveness of the Casework Workshop (1962-1963) as a training implement is being used for the pilot study.

Significance: There is a need to evaluate staff development programs in our Department and in the social work field as a whole. The profession stresses agency responsibility for postgraduate professional staff education, since social workers cannot fully encompass and integrate professional knowledge needed for competence in social agencies. As of this time, the effectiveness of such educational programs in facilitating continued learning is unknown. This project is to attempt to assess effectiveness of the specific program.

Methods Employed: The Casework Workshop was selected as the staff education unit to be observed for this pilot study because it was a small homogeneous group specifically focused on learning a particular practice skill and the program is limited in time and scope.

Performance changes will be observed over a period of time in the worker's ability to make early and accurate psychosocial diagnostic evaluation. This will be accomplished through the use of learning criteria, to assess performance specific to the diagnostic process. A schedule for abstracting the tape

recordings of the Casework Workshop sessions is used as the data collection instrument.

Major Findings: None

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Impact of Cystic Fibrosis on Family Functioning

Principal Investigator: Juanita Turk

Other Investigators: Dr. Geraldine Connor

Cooperating Units: None

Man Years (calendar year 1963)

Total: 45 hours
Professional: 35 hours
Other: 10 hours

Project Description:

This project was designed to use a self-administering questionnaire and to utilize parents whose child/children were in the Clinical Center or being seem in the Outpatient Clinic. By the method employed it was hoped to gain understanding of the many emotional, economic and physical problems that are inherent with a diagnosis of Cystic Fibrosis, a chronic, fatal disease. It is expected that this knowledge will assist the staff in working with these families and also, as there is so little in the literature on this specific illness, it is hoped that it will assist others in their understanding of family problems.

Findings indicate that the family of the CF child suffers significant emotional deprivation in several areas and that communication breakdown among family members is frequent.

This paper is scheduled for publication.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

This paper has been accepted for publications by Pediatrics.

Impact of Cystic Fibrosis on Family Functioning
Juanita Turk,
M.S.W., A.C.S.W.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Interruption Study

Principal Investigators: Evelyn Walker, Shirley Owen, Lilian Scherp, A. Robert Polcari

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1963)
Total: 175 hours
Professional: 175 hours
Other: None

Project Description:

Objectives: The purpose of this study was to determine whether a problem existed in the time scheduling of a combined casework-research activities of the caseworker on NINDB. Our experience suggested that time periods allotted to research work were subject to interruptions from telephone calls, etc., related to other responsibilities. Our interest was to determine the frequency and form of these interruptions: the extent to which these interruptions related to matters taking precedence over the research work, such as need for immediate service to a patient; and the effects of the interruptions in terms of time lost and ability of the worker to resume the research work within the time allotted.

Methods Employed: Two schedules were devised (the second a revision of the first) and used among the NINDB social service staff for six weeks, listing the number, kind, duration, and nature of the interruptions, and the allotted time for research, as well as time lost to research by interruptions. Exploration was made as to protective devices that might be set up to curb unnecessary interruptions.

Major Findings: Time for research does exist and interruptions in this time do occur but consume a small portion of the research time even considering unnecessary interruptions. Of the 600 worker hours sampled, 53½ (9%) were spent in research. Seven percent of this research time was lost to interruptions of which there were 40. Phone calls were the most frequent form of interruptions (more than half) and were usually avoidable. Eighty percent of the interruptions were avoidable, consuming only half

of the time lost to research. The reason for this was that, by definition, avoidable interruptions required no subsequent activity, whereas unavoidable interruptions (prescheduling research time and seeking coverage) were not statistically significant.

A final report is in the process of preparation.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Part Time Practitioner -- An Untapped Resource for Social Work.

Principal Investigator: Myrna M. Weissman

Other Investigators: None

Cooperating Units: None

Man Years (calendar years 1963-64)
Total: 1/6th
Professional: 1/6th
Other: None

Project Description:

The Social Work Department of the Clinical Center has, as a way of meeting its staffing needs, begun to hire a limited number of part-time social workers. This study was undertaken to determine the effect part-time work has on the worker and her relationship to the patients and other members of the team.

The use of the part time practitioner has significance for the field of social work, a profession predominated by women and suffering a chronic personnel shortage. If more part time employment were available, more married women who are trained social workers and otherwise lost to the field, might be willing to work. Little investigation so far has been undertaken to determine objectively the pros and cons of part time social work.

As a way of getting data on the problems on part time work over a period of four months, the investigator notes all incidents which occurred with patients and other staff members which appeared to be directly related to her position as a part time practitioner at the Clinical Center, NIH.

This study is now being written up and literature is being reviewed on the personnel crisis in social work, recommendations for recruitment to the field and staffing of agencies, employment of married woman and part time employment in the professions.

Serial No. CC-21
Social Work Department
The Clinical Center
Bethesda, Maryland 20014

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Social Worker as Part of the Metabolic Research Team

Principal Investigator: Myrna M. Weissman

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1963)
Total: 1/10th
Professional: 1/10th
Other: None

Project Description:

A descriptive paper has been completed on the function of the social worker on a metabolic research unit. The material for the paper was compiled from the worker's experience with patients on a metabolic study and her work with other professional members of the research team. The major findings noted were that metabolic studies make demands on the patients in terms of confinement, restriction of activity, monotony of diet, and length of stay. The patient's usual modes of reducing stress are reduced. Moreover, the patient's cooperation in these studies is absolutely essential if the regimen is to be followed. The social work method is uniquely geared to the identification and treatment of individual problems in social functioning which can be associated with the stress created by such a metabolic regimen.

Part B included -- Yes

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

This paper has been accepted for publication in the Journal of Chronic Diseases and should appear in the April or May 1964 issue.

The Social Worker as Part of a Metabolic Research Team,
Myrna M. Weissman,
Medical Social Worker

Part B

Publications

1. Basamania, B.*: The development of schizophrenia in the child in relation to unresolved childhood conflicts in the mother. In Rosenthal, D. (Ed.): The Genain Quadruplets. New York, Basic Books, Inc., 1963, pp. 449-466.

2. Hirsch, S. I.: A caseworker's view of Mr. Genain. In Rosenthal, D. (Ed.): The Genain Quadruplets. New York, Basic Books, Inc., 1963, pp. 441-448.

3. Peay, R. E.: What social services offer to patients who undergo cardiac surgery. Public Health Rep., U. S. Dept. of Health, Education, and Welfare, Public Health Service. 78: 1045-1050, Dec. 1963.

4. Quinn, O. W., Deasy, L. C., and Ellis, B. L.*: The family as seen by the community. In Rosenthal, D. (Ed.): The Genain Quadruplets. New York, Basic Books, Inc., 1963, pp. 431-437.

5. Silber, E., Hamburg, D. A., Coelho, G. V., Murphey, E. B.*, Rosenberg, M., and Pearlin, L. I.: Adaptive behavior in competent adolescents. Arch. Gen. Psychiat. (Chicago). 5: 354-365, Oct. 1961.

6. Vernick, J.: The use of the life space interview on a medical ward. Soc. Casework. XLIV: 465-469, Oct. 1963.

7. Weissman, M. M.: The social worker as part of a metabolic research team. J. Chron. Dis. 17: 443-448, May 1964.

8. Wilkie, C. H.: A study of distortions in recording interviews. Soc. Work. 8: 31-36, July 1963.

9. Yarrow, M. R., Blank, P., Quinn, O. W., Youmans, E. G., and Stein, J.: Human Aging. U. S. Dept. of Health, Education, and Welfare, Public Health Service Pub. No. 986, Wash., D.C., Govt. Printing Office, 1963.

Papers Submitted for Publication

1. Savard, R. and Walker, E.: Social functioning after surgical treatment for temporal lobe epilepsy. Accepted for publication in Soc. Work.

2. Turk, Y.: A study of families of children with cystic fibrosis. Accepted for publication in Pediatrics.

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* Former members of the Social Work Department

Papers Presented

1. Conner, G.: A study of indices of caseworker competence. National Conference on Social Welfare, Cleveland, Ohio, May 1963.

2. Conner, G.: Research consultation to social work practitioners: Parts and Process. Southern Regional Institute, National Association of Social Workers, Raleigh, North Carolina, June 1964.

3. Roatch, J., and Bunney, W.: A behavioral and edocrinological study of severe depressive disorders. American Psychiatric Association, St. Louis, Missouri, May 1963.

4. Savard, R.: The relationship between the chaplain and the social worker. Chaplains Institute, Catholic University, Washington, D. C., Nov. 1963.

5. Savard, R.: New trends, developments and methods in the development of health services. Great Lakes Regional Institute, National Association of Social Workers, Minneapolis, Minnesota, June 1964.

6. Vernick, J.: The life-space interview in crisis situations. Southwest Regional Institute, National Association of Social Workers, San Francisco, California, Oct. 1963.

7. Walsh, E. J.: Multidiscipline practice -- the application of concepts of group interaction within the team. Eastern Regional Institute, National Association of Social Workers, Richmond, Virginia, Oct. 1963.

8. Walsh, E. J.: The social workers emerging role in practice-based research. National Conference on Social Welfare, Los Angeles, California, May 1964.

PROFESSIONAL ACTIVITIES

Mrs. Carmen Amoros-Cabrera

Consultant, Federal Housing Authority and D.C. Department of Public Welfare on Research Project, "Rehabilitating D.C. Public Assistance Recipients"

Consultant, Mental Health Bureau
D.C. Department of Public Health
"Problems of Adolescents"

Mrs. Belvin R. Blandford

Member, Delegate Assembly Review Committee
National Association of Social Workers
Washington Metropolitan Chapter

Mr. David Callagy

Member, Recruitment Committee
National Association of Social Workers
Washington Metropolitan Chapter

Miss Rintha Carter

Member, Personnel Practices Committee
National Association of Social Workers
Washington Metropolitan Chapter

Mrs. Yolande Davenport

Member, Social Policy and Action Committee
National Association of Social Workers
Washington Metropolitan Chapter

Member, Committee on Community Organization Practice
National Association of Social Workers
Washington Metropolitan Chapter

Legislative Chairman, D.C. Recreation Department Pre-School Council
Prepared statement and represented Council at District Congressional Committee Hearing

Presented NIMH Familial Dysautonomia Project Report at the Annual Meeting of the Medical Board, New York Familial Dysautonomia Association

Mr. Stanley Hirsch

Member, Social Work Examination Review Board on State Merit Systems
Department of Health, Education, and Welfare

Member, Technical Advising Committee
Jewish Social Service Agency
Washington

Consultant, Montgomery County Association for Mental Health
Survey on Residential Referrals

Mrs. Melitta Leff

Member, American Group Psychotherapy Association

Mr. Robert Mahon

Member, Steering Committee
Montgomery County Health Association

Member, Rehabilitation Committee
Montgomery County Health and Welfare Council

Consultant, District of Columbia and Prince George's County
Mental Health Association on "Establishing Rehabilitation Centers"

Director, Montgomery Center for Discharged Mental Patients
Montgomery County, Maryland

Mrs. Lucia Mason

Secretary-Treasurer, Medical Social Work Section
National Association of Social Workers
Washington Metropolitan Chapter

Miss Roberta Peay

Workshop Leader Eastern Regional Institute
National Association of Social Workers

Mr. Robert J. Savard

Workshop Leader Great Lakes Regional Institute
National Association of Social Workers

Vice-President, Board of Montgomery County Family and
Children's Service

Member, Research Section, National Association of Social Workers
Washington Metropolitan Chapter

Mr. Walter Sceery

Co-ordinated and participated in a program on National Institute of Mental Health for Voice of America

Miss Ellen Walsh

Member, National Education and Practice Committee
Medical Social Work Section
National Association of Social Workers

Chairman, Subcommittee on the "Study of Intervention"
National Practice Committee
Medical Social Work Section
National Association of Social Workers

Member, Task Force on Fields of Practice
Medical Social Work Section
Commission on Social Work Practice
National Association of Social Workers

Awards Board, National Institutes of Health

Instructor, Seminar on "Theory of Supervision"
Catholic University

Civil Service Rating and Review Board
Clinical Social Workers
United States Public Health Service

Workshop Leader, Eastern Regional Institute
National Association of Social Workers

Educational Director, Southern Regional Institute
National Association of Social Workers

Mrs. Charlotte Wilkie

Member, Education Committee
National Association of Social Workers

Member, Recruitment Committee
National Association of Social Workers

Member, Family and Child Welfare Committee
National Association of Social Workers

Mrs. Charlotte Wilkie (Continued)

Member, Board of Directors
Montgomery County Mental Health Association

Delegate, Health and Welfare Council
Montgomery County Mental Health Association

Member, Health Conference
Health and Welfare Council
National Capital Area

TABLE NO. 1

Patients' Welfare Fund Expenditures

Fiscal Year 1964

	Special Programs, Prisoners, Children, etc.	Patient Transportation	Allowance to Relatives	Patients' Misc. Expenditures, Meals, Clothes etc.	Basic Necessities	Total Withdrawn
July, 1963	$ 131.09	$ 113.20	$ 1,184.50	$ 17.00	$ 386.56	$ 1,832.35
August	130.15	77.70	744.00	111.87	305.00	1,368.72
September	311.17	165.55	953.50	3.81	258.00	1,692.03
October	263.82	197.80	869.72	57.50	355.00	1,743.84
November	250.62	-	211.95	19.55	281.25	763.37
December	222.55	59.77	173.00	60.00	271.25	786.57
Jan., 1964	236.93	43.30	453.70	182.25	303.25	1,219.43
February	285.17	96.29	581.25	62.04	225.75	1,250.50
March	215.84	142.09	344.00	87.50	270.25	1,059.68
April						
May						
June						
TOTAL	$ 2,047.34	$ 895.70	$ 5,515.62	$ 601.52	$ 2,656.31	$ 11,716.49

RECAPITULATION:

Balance brought forward 7/1/63		$ 3,219.38
*Fiscal Year 1964 Deposits		10,780.50
		$ 13,999.88
Fiscal Year 1964 Withdrawals		11,716.74
Balance on Hand 3/31/64		$ 2,283.14

*Total as of the first three quarters.

TABLE NO. 2
Patients' Welfare Fund Expenditures
Fiscal Year 1963

	Special Programs, Prisoners, Children, etc.	Patient Transportation	Allowance to Relatives	Patients' Misc. Expenditures, Meals, Clothes etc.	Basic Necessities	Total Withdrawn
July, 1962	$ 298.21	$ 235.80	$ 427.50	$ 44.67	$ 226.15	$ 1,232.33
August	142.68	16.00	462.29	29.53	274.22	924.72
September	151.64	27.00	110.95	38.00	220.22	547.81
October	208.10	35.10	85.00	17.50	282.10	627.80
November	165.50	60.15	195.00	151.18	291.22	863.05
December	296.24	69.13	438.12	86.44	314.84	1,204.77
Jan., 1963	286.56	111.40	106.00	27.00	199.36	730.32
February	711.96	70.52	350.50	97.70	213.00	1,443.68
March	123.43	61.80	452.35	25.12	226.50	889.20
April	269.81	87.56	559.50	81.00	253.50	1,251.37
May	310.95	123.30	698.10	31.39	206.00	1,369.74
June	386.84	15.00	476.50	166.00	195.65	1,239.99
TOTAL	$ 3,351.92	$ 912.76	$ 4,361.81	$ 795.53	$2,902.76	$12,324.78

RECAPITULATION:

Balance brought forward 7/1/62	$ 1,672.91
Fiscal year 1963 Deposits	13,892.40
	$ 15,565.31
Fiscal Year 1963 Withdrawals	12,345.93
Balance on Hand 6/30/63	$ 3,219.38

TABLE 3

COMPARATIVE EXPENDITURES FOR ALLOWANCES TO RELATIVES FOR NCI, NHI AND OTHER INSTITUTES COMBINED FY '61-'64*

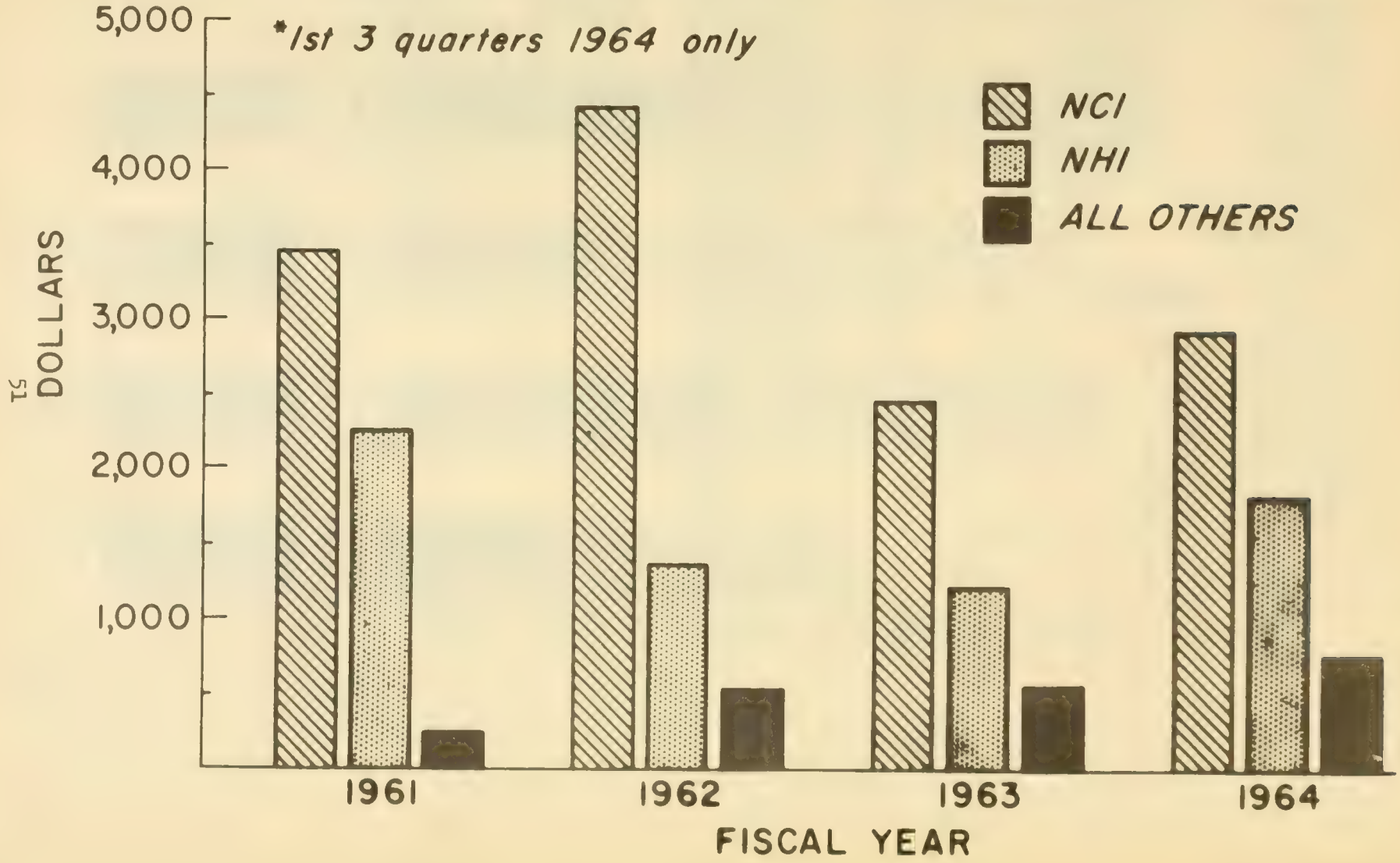
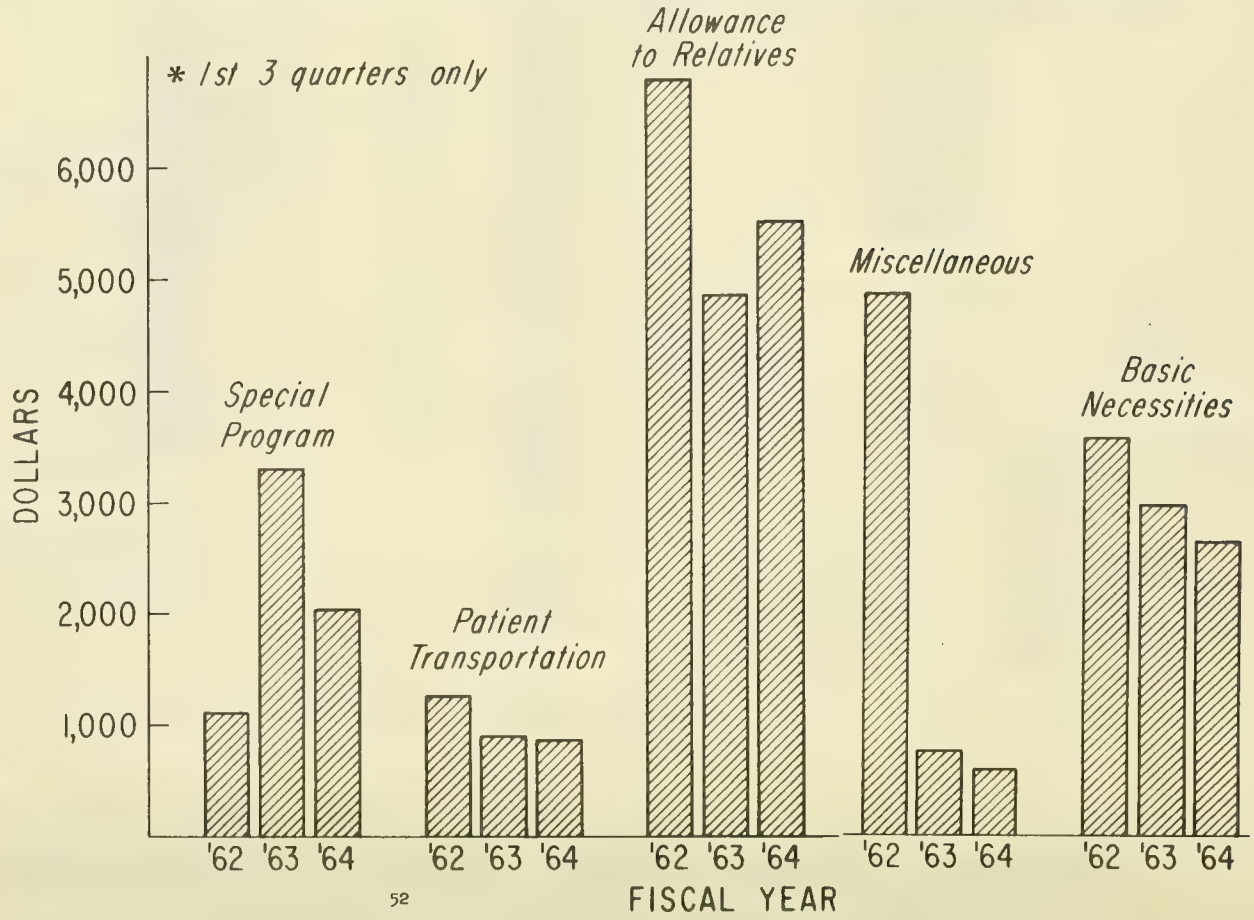


TABLE 4

PT WELFARE FUND EXPENDITURES BY CATEGORY FY '62-'64 *



PATIENT WELFARE FUND INCOME
COMPARISON OF R&W CONTRIBUTIONS TO
ALL OTHER CONTRIBUTIONS FY '61–'64

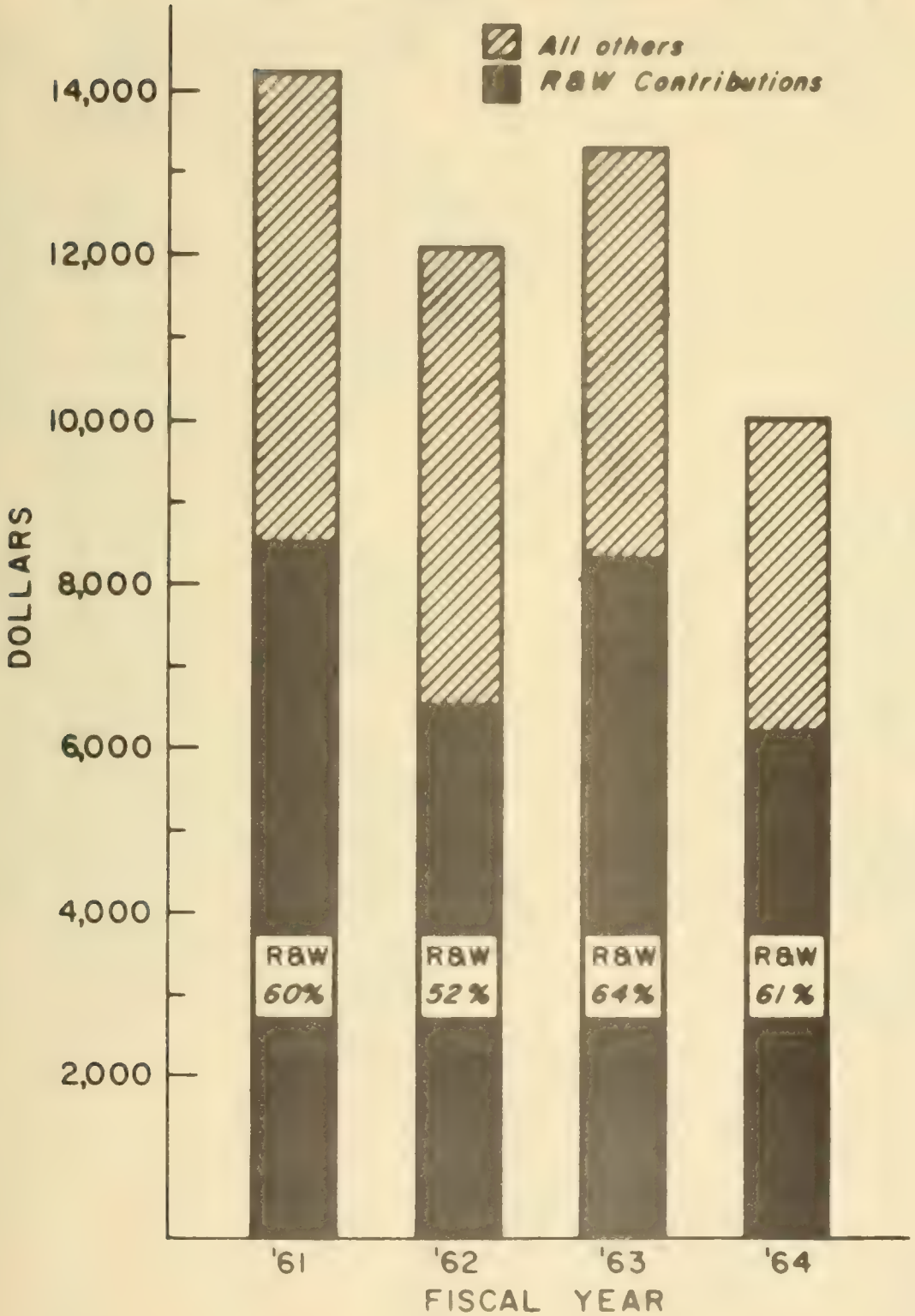
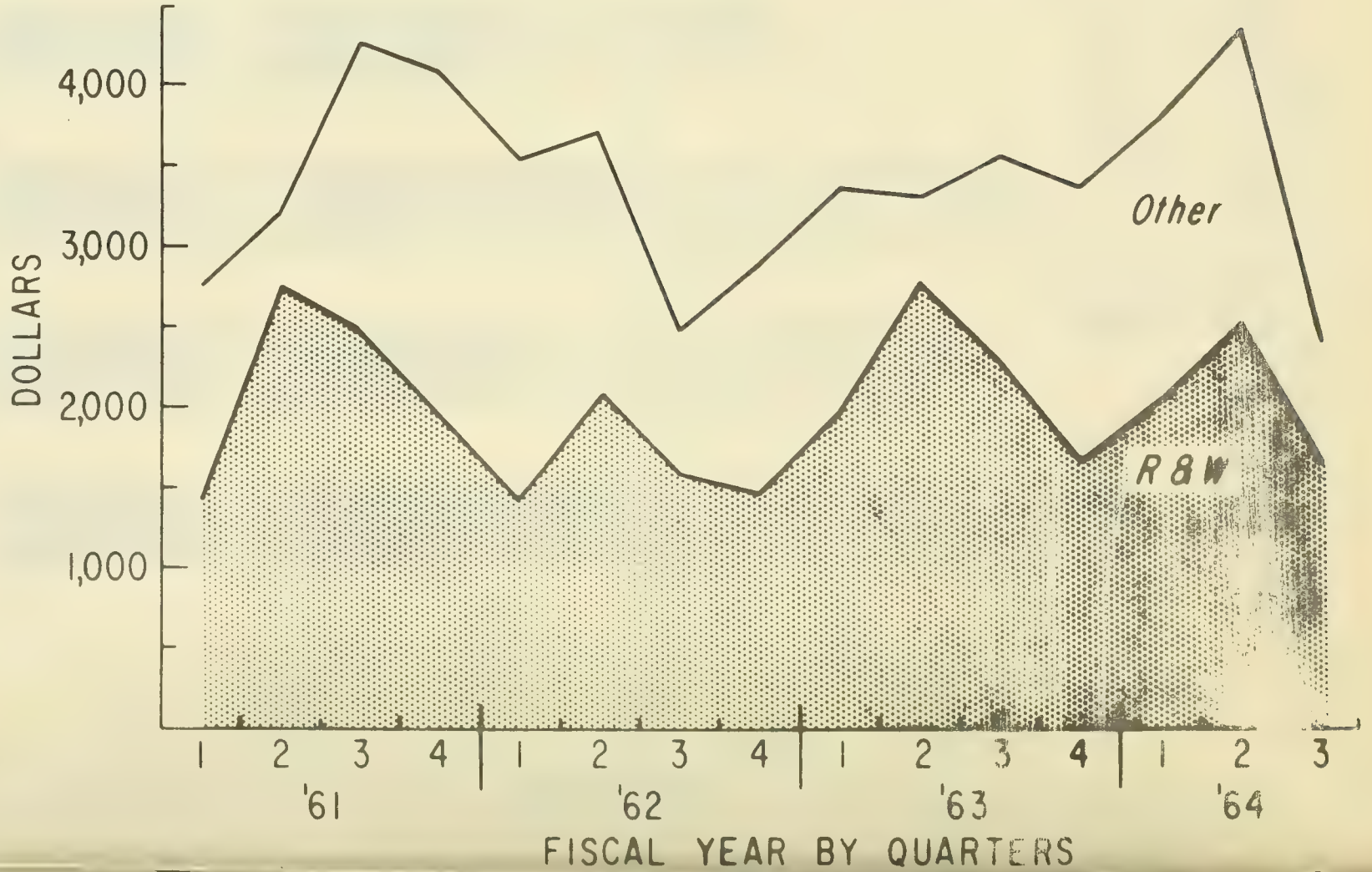


TABLE C

PATIENT WELFARE FUND INCOME
COMPARISON OF R&W CONTRIBUTIONS TO ALL OTHER CONTRIBUTIONS FY '61-'64



PT [illegible]ARE FUND
INCOME AND E[illegible]PENDITURES FY '60-'64

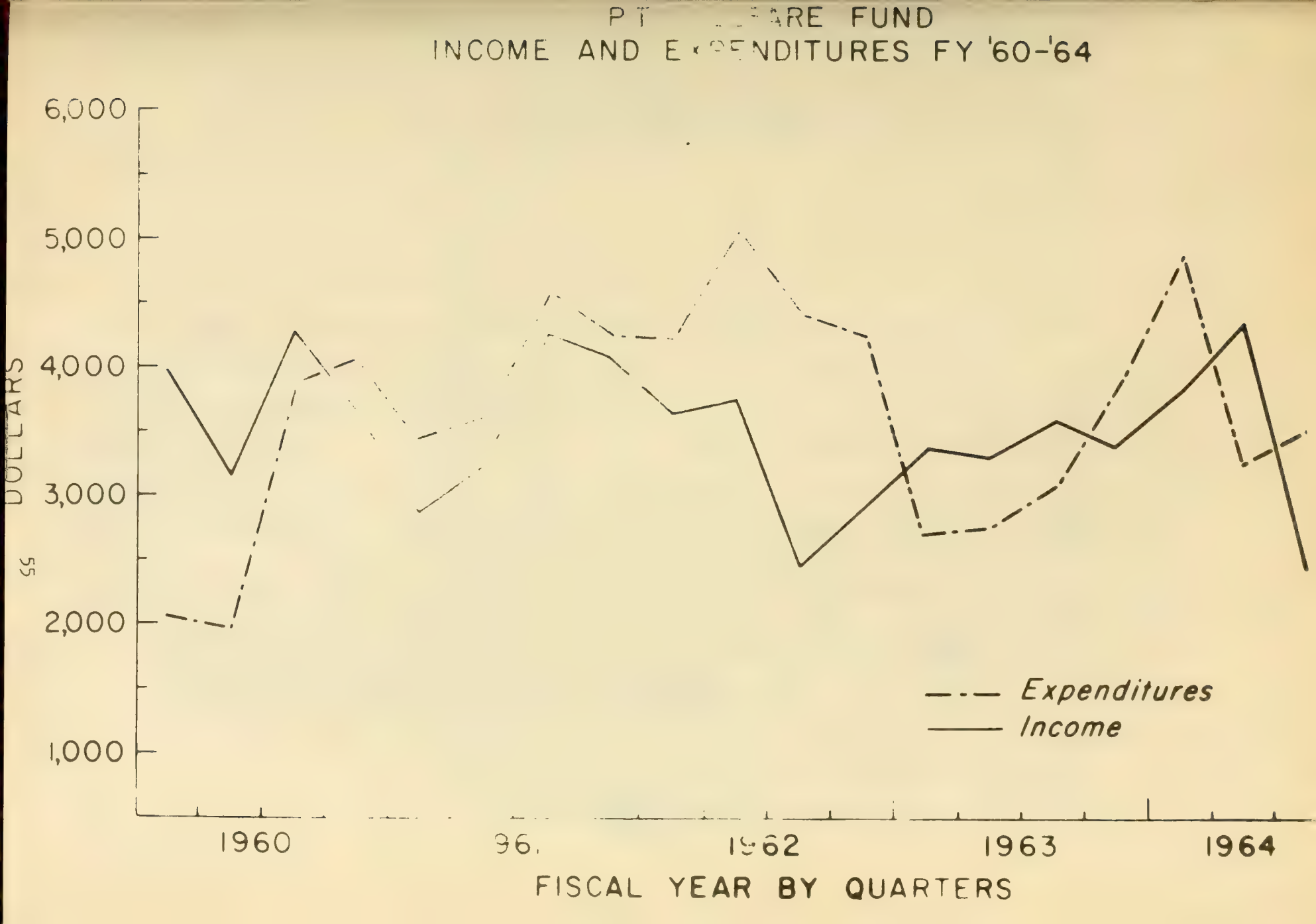


TABLE 8

Client Principal Problem
F.Y. 1964

	Hospital Experience	Reaction to Illness	Separation	Readjustment of Living Patterns	Resources	Family Relation-ships	Other
NCI	102	237	18	25	94	56	3
NHI	140	131	13	29	24	18	0
NIAMD NIAID	46	37	28	42	20	20	3
NINDB	28	35	18	29	65	31	3
NIMH	8	15	10	19	4	58	8
TOTAL	324	455	87	144	207	183	17*

*Almost insignificant number of this indicates effectiveness of categories.

TABLE 9

Social Services for In-Patients

F.Y. 1963*

Month	NCI	NHI	NIAID	NIMH	NINDB	TOTAL
1962 July	1,183	1,260	453	812	457	4,165
August	789	897	493	828	456	3,463
Sept.	932	625	430	891	302	3,180
Oct.	846	544	465	1,059	370	3,284
Nov.	887	664	450	847	211	3,059
Dec.	789	585	392	793	217	2,776
1963 Jan.	659	853	411	1,165	301	3,389
Feb.	518	628	473	1,253	312	3,184
March	384	730	382	1,289	448	3,233
April						
May						
June						
TOTAL	6,987	6,786	3,949	8,937	3,074	29,733

*Because of a lag in data processing, reports have been received for only the first three quarters of fiscal year 1963. The projected total for 12 months is 39,642 interviews.

TABLE 10

Social Services for In-Patients
F.Y. 1964*

MONTH	NCI	NHI	NIAID	NIMH	NINDB	TOTAL
1963 Jan.	1,320	694	475	699	423	3,611
Feb.	1,164	967	485	681	454	3,751
March	1,138	1,002	571	718	447	3,876
April						
May						
June						
TOTAL	3,622	2,663	1,531	2,098	1,324	11,238

*Because of a lag in data processing, reports were not available for 1st two quarters of F.Y. 1964. Data secured through a new reporting system projected from the 3rd quarter to the whole year indicates an estimate total interview count of about 44,000.

TABLE 11

GROUP ACTIVITY REPORT

Fiscal Year 1963

	RESEARCH ACTIVITIES		PRACTICE-PROGRAM ACTIVITIES		SOCIAL SERVICE DEPARTMENTAL ACTIVITIES		COMMUNITY AND PROFESSIONAL ACTIVITIES		CORPS, AND OTHER RELATED ACTIVITIES		TOTAL HOURS
	HOURS	%	HOURS	%	HOURS	%	HOURS	%	HOURS	%	
NCI	485	22	924	42	641	29	161	7	-	-	2,211
NHI	213	10	992	48	734	35	135	6	10	1	2,084
NIMH	8,344	69	2,354	19	1,010	8	467	4	3	.01	12.178
NIAMD	187	25	442	58	126	16	4	1	-	-	759
NIAID	226	22	382	37	373	36	25	3	21	2	1,027
NINDB	512	36	377	27	417	29	31	2	79	6	1,416
TOTAL	9,967		5,471		3,301		823		113		19,675

TABLE 12

SOCIAL WORK DEPARTMENT
F.Y. 1964*

	RESEARCH ACTIVITIES		PRACTICE-PROGRAM ACTIVITIES		SOCIAL SERVICE DEPARTMENTAL ACTIVITIES		COMMUNITY AND PROFESSIONAL ACTIVITIES		CORPS, AND OTHER RELATED ACTIVITIES		TOTAL HOURS
	HOURS	%	HOURS	%	HOURS	%	HOURS	%	HOURS	%	
NCI	248	12.9	926	48.2	693	36.1	54	2.8			1,921
NHI	175	8.6	924	45.1	862	42.1	72	3.5	15	.7	2,048
NIMH	5630	71.1	1,404	17.7	736	9.3	145	1.8	11	.1	7,926
NIAMD	110	14.5	293	38.7	303	40.2	50	6.5			756
NIAID	42	10.2	231	56.2	133	32.4	2	.5	3	.7	411
NINDB	153	14.9	344	33.6	479	46.7	40	3.8	11	1.0	1,027
TOTAL	6358		4,122		3206		363		40		14,089

*9 months only

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT
CLINICAL CENTER

CC-34
Serial No.

ANESTHESIOLOGY DEPARTMENT

The Anesthesiology Department is a professional service department of the Clinical Center. As such, its primary objectives and responsibilities are to provide anesthesia and related services for all Clinical Center patients. Administration of anesthesia and related supportive care for patients undergoing major operative surgery and diagnostic procedures requiring general anesthesia, and/or close surveillance of vital signs, was the major concern of anesthetist personnel. The conduct of inhalation therapy, which included the administration of oxygen, humidified atmospheres and aerosols, and techniques for maintaining and supporting respiratory function, was the responsibility of our Inhalation Therapy Section. In addition to these service functions, research studies were carried out by staff anesthesiologists when time from clinical duties and laboratory facilities were available. Collaborative studies were done with investigators of NHI, NINDB and NIDR.

The full-time staff consisted of several categories of professional, subprofessional, and clerical personnel as listed below. The numbers indicated below are based on the yearly average during calendar year 1963.

*Clinical Anesthesiologists	7
**Visiting Program Anesthesiologist	½
***Research Anesthesiologist	1
Nurse Anesthetists	3
Inhalation Therapists	4
****Extracorporeal Apparatus Technicians	2½
Anesthesia Technicians	3½
Secretaries	2

Outside consultants' services were utilized on an occasional basis.

I. ANESTHESIOLOGICAL PROCEDURES. Anesthesia and supportive therapy were carried out in a total of 1182 instances for 875 surgical operations and 307 diagnostic procedures. In addition, diagnostic nerve blocks, consultations for respiratory and pain problems and emergency resuscitation measures performed outside of surgical areas, totaled 109.

A large proportion of the relatively complex surgical operations and diagnostic procedures performed at the Clinical Center required the maintenance

* Devoted minimum of one day per week to research.
** Devoted half time to laboratory research, NINDB.
*** Two senior anesthesiologists devoted half time to laboratory research.
**** Assigned to Anesthesiology Department for administrative purposes.

of anesthesia over unusually long periods of time. For example:

Anesthesia time exceeded 3 hours in 495 operations (42%)
Anesthesia time exceeded 5 hours in 197 operations (17%)
Anesthesia time exceeded 6 hours in 218 operations (18%)

Surgical operations were classified as follows, according to the type of surgery; special adjunctive techniques were employed as indicated:

1.	Thoracic (cardiac, pulmonary, great vessels, superficial chest)	
	a. extracorporeal circulation technique	164
	b. usual technique	97
2.	Neurosurgical (brain and skull)	
	a. hypothermia technique	9
	b. usual technique	52
	c. stereotaxic procedures, thalamotomies	41
	d. spinal cord	7
	e. others	1
3.	General surgical (abdominal, pelvic and inquinal)	
	a. hypothermia technique	1
	b. usual technique	110
4.	Kidney operations including bladder and adrenal gland	44
5.	Perineal (gyn-31, genito-urinary-30, others-4)	65
6.	Head, neck, and face	69
7.	Eye, ear, nose, and throat	23
8.	Dental (majority with detailed physiological monitoring).	135
9.	Orthopedic	28
10.	Miscellaneous procedures	29
	Total	875

Most of the surgery performed at the Clinical Center is concerned with such procedures as radical excision surgery for treatment of cancer of the pelvic organs and face and neck structures; cardiac surgery for correction of congenital and acquired defects with the aid of a pump oxygenator, (so that the heart and lungs are bypassed during the period of definitive surgery), and surgery on the brain consisting of localization and removal of irritative foci as well as the removal of intercranial tumors with the aid of hypothermia. Included were 41 stereotaxic procedures for treatment of syndromes characterized by abnormal movements and rigidity, a considerable increase over the 24 procedures done last year. Operations entailing the use of extracorporeal circulation were carried out in 164 instances, whereas hypothermia techniques were employed in 8 operations, approximately the same as during the previous year. The preponderance of lengthy complex surgical procedures required the attendance of two professional anesthetists, and, the services of trained anesthesia technicians were necessary for the assembly and operation of monitoring equipment, thermal devices, and accessory equipment. A relatively large number (135) of short duration dental procedures, where elaborate physiological monitoring was carried out, also required two anesthetists and one

technician for their conduct.

Diagnostic studies done under anesthesia numbered 307. Many of the patients were small children who were unable to cooperate under local anesthesia. Methods of controlled sedation over periods of several hours were required for cardiac catheterization studies. Other tests done on adults required general anesthesia and complete muscular paralysis and respiratory control during selected periods. Since many of these patients were ill and the manipulations during the tests were capable of causing serious cardiac or respiratory reactions, special care was required in the anesthesiological management. Diagnostic tests done under general anesthesia are tabulated below:

Pneumoencephalograms	56
Cerebral angiography	60
Special eye or ENT examinations	6
Cardiac catheterization procedures	91
right heart catheterizations	48
trans-septal or percutaneous left heart catheterization	5
right heart catheterizations and angiography	29
angiocardiography or aortography	9
Cystoscopy, including 16 renal function tests	42
Miscellaneous	52

The following table indicates the institutes responsible for the admission of surgical patients requiring anesthesia. The first four institutes listed have surgical services.

Sponsoring Institute	Procedures	Percent
NHI	426	36%
NCI	285	24%
NINDB	275	23%
NIDR	128	11%
NIAMD	45	4%
NIAID	16	1%
NIMH	7	½%

Surgical and diagnostic procedures requiring the services of anesthetists were divided between the four Institute surgical services as follows:

	Procedures	Percent
NHI	*396	33%
NCI	374	32%
NINDB	**276	23%
NIDR	136	12%

*includes 91 cardiac catheterization procedures
**includes 116 radiographic diagnostic procedures

II. INHALATION THERAPY ACTIVITIES. Inhalation therapy treatments were carried out by or under the direction of inhalation therapists. Consultation service was provided by an assigned anesthesiologist. The numbers and types of treatments during 1963 were:

Oxygen therapy (tent, mask, catheter)	3,576 hours
Humid atmosphere therapy	44,442 hours
Aerosol therapy	2,870 treatments
Intermittent positive pressure breathing with aerosols	9,092 treatments
Long-term respiratory assistance	9,657 hours
Short-term resuscitation	555 hours
Administration of oxygen combined with other gases (carbon dioxide, helium)	203 treatments

A significant increase in the use of long-term respiratory assisting devices was noted during the year with the total number increasing from 4,553 hours to 9,657 hours.

The continued trend toward the performance of operations of a more formidable nature, in which complete replacement of heart valves are becoming more common, accounted for the use of respiratory assisting devices over relatively long periods of time. There was also a noteworthy increase in the administration of aerosolized medications by means of intermittent positive pressure breathing devices (9,092 treatments as compared to 5,901 treatments in 1962).

Improved and expanded facilities for gas sterilization (ethylene oxide) of all types of inhalation therapy equipment, including large units such as oxygen tents, were installed in the workroom of the Inhalation Therapy Section. Economy in time and materials and more efficient handling of contaminated equipment has resulted from this arrangement.

A total of 157 new employees of the Nursing Department attended regularly scheduled demonstration sessions for the purpose of acquainting them with inhalation therapy practices and equipment. Special demonstrations of tank respirators, intermittent positive pressure breathing devices, and techniques of exhaled air resuscitation were conducted for 116 other employees.

III. RESEARCH ACTIVITIES. Members of the Anesthesiology Department participated in both clinical and basic laboratory research during the eighteen month period included in this report. In both instances the investigative activities were carried out through the close cooperation of personnel from one of the Institutes. The Anesthesia Research Unit, established in July 1962, by agreement with the Surgical Branch of the NHI, continued to provide facilities for studies of the basic pharmacology and physiology of anesthetic drugs. This facility in Building 3 was utilized by Drs. D. H. Morrow and N. T. Townley during 1964. In addition, the Section on Clinical Biophysics, Cardiology Branch, NHI, provided laboratory facilities for another member of our department, Dr. L. J. Thomas. Individual project reports in which members of the Anesthesiology Department were the principal investigators are attached.

Anesthesiology Department

Summaries of the investigative projects involving members of this department, which were carried out during the period of this report are:

1. General Anesthesia for Dental Outpatients. A long-range study concerned with the investigation of the physiological changes which occur during the use of various types of general anesthesia in office patients undergoing multiple dental extractions was continued. A number of intravenous anesthetic agents have been studied during previous years in an effort to determine which was the most suitable for dental ambulatory patients. During the current year, studies were made on the effects of halothane in combination with small doses of intravenous barbiturates and nitrous oxide.

Attention was also directed toward the refinement of the methods used to monitor blood pressure, pulse, arterial blood oxygen saturation, and other parameters which are measured continuously during anesthesia and surgery.

2. Anesthesia and Digitalis Toxicity. An Experimental Study. These animal studies indicated that the relationship between the therapeutic and toxic levels of digitalis may be significantly modified by anesthetic drugs. (Dr. D. H. Morrow and Dr. N. T. Townley)

3. Systemic Venous Reactivity: An Experimental Study in the Dog. A study which led to the development of a stable animal preparation by means of which reflex venous reactivity can be assessed independent of changes in arterial flow. (Dr. D. H. Morrow and Dr. G. E. Pierce, NHI)

4. Effects of Halothane Inhalation Anesthesia on Systemic Venous Reactivity: An Experimental Study in the Dog. An investigation, utilizing the preparation described above, which demonstrated that 2.5% halothane anesthesia produces a 20% to 50% reduction in reflexly induced venous constriction. (Dr. D. H. Morrow and Dr. G. E. Pierce, NHI)

5. The Responses to Anesthesia of Non-hypertensive Patients Pretreated with Reserpine. A clinical stuay which indicated that the bradycardia and profound hypotension which have been reported during anesthesia in patients receiving reserpine may be related to their underlying hypertensive disease rather than the rauwolfia therapy. (Dr. D. H. Morrow and Dr. A. G. Morrow, NHI)

6. Chronotropic and Inotropic Effects of Halothane Upon Catecholamine Depleted Dogs. A study which showed that the cardiovascular responses to halothane anesthesia of patients receiving guanethedine therapy for hypertension should be similar to those determined in patients receiving reserpine. (Dr. J. Rein, Dr. D. H. Morrow, Dr. G. Austen, NHI)

7. Coarctation of the Aorta. The relationship of repair on the systemic vasculature. A collaborative effort by Dr. D. H. Morrow with Dr. J. S. McLaughlin and Dr. A. G. Morrow, NHI, designed to further elucidate the etiology of "paradoxical hypertension" occurring after repair of coarctation of the aorta.

8. The Effect of Anesthetic Gases on the Hypoxic Response of Pressure, Flow and Resistance in the Pulmonary Vasculature. A study which indicates that halothane anesthesia decreases the pulmonary venous constrictive response to hypoxia and that the magnitude of this decrease is a dose dependent phenomenon. A collaborative study involving Dr. D. H. Morrow and Dr. M. Buckley, et al., NHI.

9. National Halothane Study. A detailed retrospective analysis of anesthetic administration during the four year period, January 1959 to December 1962. The Anesthesiology Department is participating with twenty-one other institutions in this evaluation of the possible hepatotoxic effects of various anesthetics including halothane. The national scope of this study is being sponsored by the NIGMS. (Dr. J. Plumlee, Dr. D. H. Morrow and Dr. W. Dixon)

10. The Concept of Pulmonary Vascular Resistance Where Intra-alveolar Pressure Exceeds Venous Pressure. An extension of observations on the perfused excised dog lung preparation made previously by this investigator in a physical model. The scope of this study represents a detailed attempt to demonstrate the physical forces involved in the "vascular waterfall" and to define its importance. (Dr. L. J. Thomas, and Dr. D. L. Fry, NHI)

11. Studies on the Effect of End Expiratory CO_2 on Cerebral Angiograms in Patients with Intracranial Tumors. A collaborative study undertaken by Dr. L. J. Thomas with Dr. T. Krueger, NINDB, and Dr. D. Rockoff CC, Radiology. Preliminary findings suggest that differential tumor "staining" is significantly better when end expiratory CO_2 is low, rather than high or normal.

12. The Sequestration of Blood during Cardiopulmonary Bypass. A study designed to elucidate the magnitude and possible preventive therapy for the loss of blood from the active circulation during extracorporeal circulation. A collaborative study by Dr. J. Plumlee and Dr. G. E. Pierce, NHI.

13. The Clinical Effects of Droperidol and Fentanyl as Agents for Premedication and Anesthetic Supplementation. A study designed to evaluate these pharmacologic agents in patients being operated upon under local anesthesia. (Dr. P. Mann and Dr. C. Hebert)

IV. MAJOR PROBLEMS ENCOUNTERED. No serious problems were encountered during the period covered by this report. However, the recruitment of trained personnel, both professional and sub-professional, required a

disproportionate amount of time and effort in comparison with the small size of our organization. The opening of the new surgical wing, Building 10 A, presented logistics problems and added new responsibilities.

A. Personnel recruitment

1. Anesthesiologists. As in previous years, heavy reliance was placed on the PHS CORD Program to supply us with trained anesthesiologists. Five out of the eight anesthesiologists on our staff fall in this category. After serving two years, these physicians invariably leave to accept staff appointments at universities or enter private practice because of more attractive financial arrangements outside of NIH. The loss, through accidental death, of a member of our senior career staff, Dr. G. R. Christenson, left a vacancy which could not be filled with an anesthesiologist of equivalent professional stature. By increasing the opportunities for laboratory research, some improvement in employment incentives has occurred but the government scale of remuneration remains woefully inadequate in comparison with outside opportunities.

2. Extracorporeal circulation apparatus operators. Considerable difficulty was encountered in the recruitment of technical personnel with suitable academic and experience background to qualify them for the responsibilities of operating extracorporeal apparatus. During the reporting period, problems arose during the prolonged illness of of one of the two incumbents and as the result of progressively longer and more complex surgical procedures. Extraordinary long hours of work were required during four out of five days when open heart procedures are scheduled. An attempt was made to train a candidate who proved not to be suitable for this type of work. This added considerably to the work of the incumbents. Present civil service grade of the extracorporeal apparatus operators is GS-7. Revised job descriptons incorporating current duties and responsibilities as they have been expanded from those allotted to the position over two years ago, were submitted in an effort to obtain a grade which would be more commensurate with the work performed by the two regular incumbents.

B. Logistics problem.

The addition of the new surgical wing containing two operating rooms and one Cardiac Catheterization Laboratory on the second floor and two operating rooms on the fourth floor added 5 more anesthetizing locations to the potential 12 other anesthetizing locations located in the main Clinical Center. Because it was not feasible to supply these added locations from the main anesthesia workroom, each of the four new operating suites were made self-sufficient from the standpoint of equipment, material and drugs. Consequently, the number of anesthesia technicians, who are charged with the responsibility of reconditioning and maintaining anesthetic supplies and apparatus, consequently had to be increased. Communication between the central

office of the Anesthesiology Department and the outlying surgical suites is not entirely satisfactory, particularly after regular working hours when secretarial personnel are not available.

V. CHANGES AND IMPROVEMENTS, AND FUTURE OBJECTIVES

1. Nurse anesthetists. Senior nurse anesthetists trained to perform special duties in conjunction with the management of patients during extracorporeal circulation and general body hypothermia were given recognition through a one grade increase in their Civil Service rating. A two grade increase was secured for the position of Nurse Anesthetist Supervisor. The upgrading of these positions represents well deserved recognition of the important responsibilities entrusted to nurse anesthetists of proven ability.

2. Sterilization of inhalation therapy and anesthetic equipment. Through the aid and cooperation of the Environmental Services Branch improved methods of gas sterilization of inhalation therapy equipment and liquid chemical sterilization of anesthesia equipment have been developed and put into routine use. The material from which inhalation apparatus is constructed and the mechanical nature of many of these items make ordinary methods of sterilization unsuitable. The possible detrimental effects of organisms found in ordinary tap water on the health of patients is difficult to assess, in view of the experience during past decades in which ordinary soap and water cleansing has constituted the chief method of reconditioning this type of equipment. Since ordinary tap water contaminant organisms rapidly multiple whenever the water is allowed to stagnate, it seems quite essential that we should take all possible precautions to protect patients, who may be unduly susceptible to infection because of their medical status, from undue exposure to such organisms even though the pathogenicity for such organisms in the healthy person is extremely low.

3. Anesthesia training for outside physicians. Through special arrangements with Providence Hospital of Washington, D. C. and Sinai Hospital of Baltimore, Maryland, three senior anesthesia residents were assigned to the Clinical Center to obtain experience in the management of patients undergoing open heart surgery, under the immediate direction of our staff anesthesiologists. The lack of routine surgical cases of a diversified nature makes it impossible to establish a basic residency training program at the Clinical Center. Currently, the Anesthesiology Specialty Board is in the process of increasing its requirements to a total of three years of approved training. For this reason, we may have an increasing number of requests for affiliated training from nearby institutions with approved anesthesia residencies.

4. Future objectives. The primary objectives for the future development and stabilization of the Anesthesiology Department are concerned with the recruitment of qualified career personnel so that less dependenc

will have to be placed upon newly trained anesthesiologists fulfilling their military obligations. Continuing efforts are being made to attract experienced personnel within the framework of the conditions of employment which pertain to the Anesthesiology Department of the Clinical Center.

VI. ARTICLES AND PRESENTATIONS

A. Articles published

1. Hebert, C. L.: Anesthesia. In Cantor, P. D. (Ed.): Traumatic Medicine and Surgery for the Attorney. Washington, Butterworth, 1963, vol. 9, pp. 357-385.

2. Morrow, D. H. and Morrow, A. G.: The responses to anaesthesia of non-hypertensive patients pretreated with reserpine. Brit. J. Anaesth. 35: 313-316, May 1963.

3. Morrow, D. H., Gaffney, T. E., and Chidsey, C. A.: The effect of norepinephrine infusion on reserpine-induced myocardial catecholamine depletion: I mplications in anesthesiology. Anesth. Analg. (Cleveland) 42: 21-24, Jan.-Feb. 1963.

4. Morrow, D. H., Gaffney, T. E., and Chidsey, C. A.: Reversal of reserpine induced myocardial catecholamine depletion by norepinephrine infusion: Implications in anesthesiology. Anesth. Analg. (Cleveland) 42: 21-24, Jan.-Feb. 1963.

5. Morrow, D. H., Gaffney, T. E., and Braunwald, E.: Studies on digitalis VII: Influence of hyper and hypothyroidism on the myocardial response to ouabain. J. Pharmacol. Exp. Ther. 140: 324-328, June 1963.

6. Morrow, D. H., Gaffney, T. E., and Braunwald, E.: Studies on digitalis VIII: Effect of autonomic innervation and of myocardial catecholamine stores upon the cardiac action of ouabain. J. Pharmacol. Exp. Ther. 140: 236-242, May 1963.

7. Rein, J., Austen, G., and Morrow, D. H.: Effects of guanethidine and reserpine on the cardiac responses to halothane. Anesthesiology 24: 672-675, Sept.-Oct. 1963.

8. Sprouse, J. H., Galindo, A., and Morrow, A. G.: Influence of various drugs and anesthetic agents on cardiac excitability in man. Anesthesiology 24: 120, Jan.-Feb. 1963.

9. Suutarinen, T.: Anesthesia at the children's hospital, University of Helsinki. J. Am. A. Nurs. Anes. 31: 229-235, Aug. 1963.

10. Morrow, D. H. and Townley, N. T.: Effects of anesthesia on digitalis toxicity. Surgical Forum 14: 240-242, 1963.

11. Driscoll, E. J., Christenson, G. R., and White, C. L.: Ambulatory dental surgery-a resume of four years experience. J. All Surg., Anesth. Hosp. Dent. Ser. (In press.)

12. Fitzwater, J. L. and Hebert, C. L.: The circular surgical wing at NIH. Amer. J. Nurs., May 1964.

13. Morrow, D. H.: Methods for measuring ventricular performance and the effects of anesthetic drugs on ventricular function. To be included in book entitled "Effects of Anesthetics on the Circulation". (In press.)

B. Presentations

1. Morrow, D. H. and Townley, N. T.: Effects of Anesthesia on Digitalis Toxicity.
Presented: Surgical Forum Session of American College of Surgeons, San Francisco, California, Oct. 27, 1963 - Nov. 1, 1963. Abstract published in Surgical Forum Vol. XIV, 1963.

2. Morrow, D. H.: Anesthesia and Digitalis Toxicity: An Experimental Study.
Presented: 38th Congress of the International Anesthesia Research Society, Las Vegas, Nevada. (In press, Anesth. Analg.)

3. Morrow, D. H.: Methods for Measuring Ventricular Performance and the Effects of Anesthetic Drugs on Ventricular Function.
Presented: National Academy of Sciences, May 23-24, 1964, Washington, D. C.

4. Sprouse, J. H.: Newer Concepts in Electrical Anesthesia.
Presented: Annual Meeting, Association of Operating Room Nurses, Washington, D. C., February 18, 1963.

5. Hebert, C. L.: Hypothermia, Its Development, Current Use and Future Trends.
Presented: Annual Meeting, Association of Operating Room Nurses, Washington, D. C., February 18, 1963.

6. Hebert, C. L., Morrow, D. H., and Sprouse, J. H.: Anesthesiologists in Wonderland.
Presented: Meeting of Maryland-District of Columbia Society of Anesthesiologists, Washington, D. C., December 1963.

7. Christenson, G. R.: Exhibit on Hypothermia Techniques and Methods of Physiological Monitoring During Hypothermia
Presented: Association of Operating Room Nurses, Washington, D. C., February 18-20, 1963.

Serial No. CC-34
1. Anesthesiology Dept., CC
2. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Effects of Fluothane Inhalation Anesthesia on Systemic Venous Reactivity: An Experimental Study in the Dog

Principal Investigator: Dean H. Morrow, M.D.

Other Investigator: George E. Pierce, M.D.

Cooperating Unit: National Heart Institute

Man Years
Total: .50
Professional: .25
Other: .25

Project Description:

The effects of Fluothane on many aspects of cardiovascular dynamics have been well studied. The possible effects of Fluothane on the venous system, however, have received little attention. This project was designed to study the effects of Fluothane on reflex venoconstriction in the dog.

The preparation employed in this study is described in another project from our laboratory (calendar year 1963). The aorta, pulmonary artery, inferior vena cava and superior vena cava were simultaneously occluded at their communications with the heart and, at the same time, a large cannula in the aorta was opened to lower the arterial pressure to zero (atmospheric pressure). Within 10 seconds reflex venoconstriction secondary to hypotension produced a marked rise in caval pressure which reached a maximum within 20-30 seconds. The occlusive clamps were then released and within five minutes pressure and heart rate returned to control values. A mixture of Fluothane 2.5% with oxygen was given via a Frumin respirator for two to three minutes prior to total vessel occlusion, producing a drop in arterial pressure of approximately 20%. Fluothane runs were alternated with control runs every ten minutes for a total of about ten runs in each dog.

We have found that Fluothane causes a 20 to 50% reduction in the rate of rise and in the magnitude of the overall rise in inferior vena caval pressure.

Proposed Course: The study is near completion and will be published.

Part B not included.

Serial No. CC-34

1. Anesthesiology Dept., CC
2. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Anesthesia and Digitalis Toxicity: An Experimental Study

Principal Investigator: Dean H. Morrow, M.D.

Other Investigators: Normand T. Townley, M.D.

Cooperating Units: National Heart Institute, Cardiovascular Laboratory

Man Years (calendar year 1963)
Total: 0.04
Professional: 0.04
Other: 0

Project Description:

There has been considerable controversy regarding the advisability of digitalizing patients with questionable cardiac reserve prior to the administration of anesthesia. There has been, however, no investigation to determine whether the type of anesthetic drug being administered to a specific patient has an influence on the dose of digitalis required when acute digitalization is required during the course of surgery. All general anesthetic drugs are known to result in some degree of depression of the myocardium, and one anesthetic compound, halothane, now in widespread usage has been reported as capable of producing "failure" of the myocardium. The present study was undertaken to determine whether or not comparable depths of anesthesia produced with various drugs would influence the toxic dose of ouabain.

It has been determined that in the intact dog anesthetized with Pentobarbital 50 mg/kg, a dose which will just abolish the inner canthal eyelid reflex, that 50 ug/kg of ouabain, administered as a continuous infusion, is required to produce multiple premature ventricular contractions. It has been further determined that in these same animals, anesthetized with one percent halothane-oxygen, after a one-week rest period the dose of ouabain required to produce similar ventricular toxicity is approximately 100 ug/kg. This is true regardless of which anesthetic drug is administered to the animal first.

Proposed course of project:

It is planned that this project will be extended to include comparison of the toxic doses of ouabain required in dogs anesthetized with relatively deeper levels of these anesthetic drugs. From these observations, it is anticipated that pertinent clinical implications may be drawn regarding the influence of the individual anesthetic drugs, and the dose of these drugs, on the response of the individual patient during acute digitalization in the operating room.

Part B not included.

Serial No. CC-34
1. Anesthesiology Dept., CC
2. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Systemic Venous Reactivity: An Experimental Study in the Dog

Principal Investigator: Dean H. Morrow, M.D.

Other Investigators: George E. Pierce, M.D.

Cooperating Units: National Heart Institute

Man Years:
Total: .50
Professional: .25
Other: .25

Project Description:

The role of venous reactivity in cardiovascular dynamics is now widely appreciated. It is well established that veins react to a number of stimuli and thus reactivity has been studied quantitatively in small venous segments. No method is available, however, for quantitative study of reactivity in large venous beds. During the past year we have studied the Bartlestone preparation - an experimental method specifically designed to demonstrate constriction in large venous beds. In this preparation an attempt is made to divide the systemic circulation into two independent parts by simultaneously clamping the aorta just below the left subclavian artery and the inferior vena cava at its communication with the right atrium. (The azygos vein and external mammary vessels are previously ligated). We have found, however, that there is a significant flow of blood (100 to 200 cc./min.) between the cephalad and caudal circulations and that interventions in the cephalad circulation directly affect the inferior vena caval pressure. For these reasons the Bartlestone preparation seems to be unsatisfactory for quantitative studies. Venous reactivity has also been studied in preparations employing cardiopulmonary bypass; however, this approach also fails to eliminate shunting between the arterial and venous beds.

The present experimental study was designed to develop a preparation in the dog which will eliminate these problems. This preparation permits quantitative assessment of the effects of drugs and physiological interventions on the reactivity of the isolated total systemic venous bed.

Dogs were anesthetized with warmed intravenous chloralose and respirations were maintained with 100% oxygen. Femoral artery inferior and superior caval pressures were continuously recorded. Through a left thoracotomy, tapes were passed around both cavae and around the aorta and pulmonary artery at their origins. The azygos vein was ligated and a large cannula passed into the aorta through the left subclavian artery.

The aorta, pulmonary artery, inferior vena cava and superior vena cava were then simultaneously occluded (TVO: total vessel occlusion) and the aortic cannula opened. Within five seconds the arterial pressure fell to zero and the inferior vena cava and superior vena cava pressures rose and leveled off at plateau values. Within 10 seconds after TVO a large secondary rise in caval pressure occurred reaching another plateau within 30 to 40 seconds following TVO. The clamps were then released and within 5 minutes arterial and venous pressures and heart rate returned to control values.

The preparation is stable and as many as 20 runs over a period of 2 - 3 hours may be made in one animal with good reproducibility.

The secondary rise in caval pressure is clearly due to constriction of systemic veins and we have demonstrated that this constriction is for the most part reflexly induced. The contribution of arteries is eliminated by opening the aortic cannula. The possibility that skeletal muscular contractions may contribute has been eliminated by the administration of succinylcholine prior to each run. Splenectomy does not significantly diminish the response. Arterial pO_2, pCO_2 and pH remain constant throughout each run. The response was greatly decreased by vagotomy and bathing the carotid bodies with xylocaine or by previous catecholamine depletion with reserpine. After vagotomy and bathing carotid bodies with xylocaine a comparable rise in caval pressure may be obtained by the venous infusion of 300 to 400 cc of blood. This demonstrates the great amounts of blood which can be returned to the heart by systemic venous constriction.

Proposed Course:

We are now ready to submit a description of this preparation for publication.

Part B not included.

Serial No. CC-34
1. Anesthesiology Dept., CC
2. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Concept of Pulmonary Vascular Resistance Where Intra-alveolar Pressure Exceeds Pulmonary Venous Pressure

Principal Investigator: Lewis J. Thomas, Jr., M.D.

Other Investigators: Donald L. Fry, M.D.

Cooperating Units: National Heart Institute

Man Years
Total: 0.4
Professional: 0.1
Other: 0.3

Project Description:

Objectives:
Critical evaluation of the contention concerning the most meaningful expression of pulmonary vascular resistance under conditions where intra-alveolar pressure exceeds pulmonary venous pressure: pulmonary arterial minus alveolar pressure divided by flow (the "waterfall" concept) versus the more conventional arterial minus venous pressure divided by flow.

Methods Employed:
A physical model designed to approach hydrodynamically an appropriate segment of the pulmonary vasculature has been used to achieve a first order approximation of flow behavior. Attempts are now being made to test the applicability of this flow behavior to excised and perfused dog lungs using established techniques.

Major Findings:
Previous work by the principal investigator as well as by others has shown that flow becomes independent of venous pressure when venous pressure is less than alveolar pressure. The model employed shows this behavior which is essential to, but by no means proof of the "waterfall" concept.

For the model, it has been possible to quantitate energy losses across the system due to viscous and kinetic components. This is necessary for evaluation of both expressions for resistance. Much has been learned about how to approach a similar analysis for the lung, but some technical difficulties remain to be overcome.

Significance to Bio-medical Research and the Program of the Institute:
When the pressure conditions mentioned above obtain for the lung, perplexing pressure-flow relationships (v.s.) have been observed. This has prompted the "waterfall" hypothesis which is a disturbing departure from the conventional, yet somewhat chameleonic, concept of vascular resistance. If it can be established that there is a sound physical basis for this departure it will then represent a contribution to the understanding of the pulmonary circulation. If it should prove unsound it will represent a dangerous source of confusion.

Proposed Course of Project:
Further attempts to demonstrate the nature of energy losses occurring across the pulmonary vascular bed in excised dog lungs.

Part B not included.

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

DIAGNOSTIC X-RAY DEPARTMENT

CC-35
Serial No.

Program Goals

The primary objective of the Diagnostic X-ray Department is to provide the highest quality complete diagnostic radiological and diagnostic radioisotope services for the patients of the Clinical Center and NIH employees. Diligent efforts will be continued to attain maximal consideration for the patient as well to increase the efficiency of the management of our program.

Additional goals include greater emphasis on the need for applied research which can be pursued within a clinical service structure and result in significant contributions to the field of radiology.

Developments and Trends

A new type of film is being developed which will revolutionize the X-ray business if it meets all of the criteria that are proposed and deemed feasible. This film is predicted to have the following advantages: a speed forty times faster than the fastest presently available film; a shelf life of 20 years; a very rapid dry process development; and a non-reactivity to environmental radiation so it may be used during atomic warfare. The stage of development is shrouded by the utmost secrecy but ultimate success is anticipated.

A trend is developing to interchange the locations of the fluoroscopy tube and the camera chain on the image intensified television monitored fluoroscopy units. As originally designed, almost all of the units except Cinelix have the very large and bulky camera chain over the X-ray table and the compact fluoroscopy tube under the table. By reversing the locations, a far more versatile unit results.

Several companies are now marketing direct positive single emulsion film with simple solarizing units containing fluorescent lights. Copies of chest films with this unit are fair to good. For all other body areas copied from films, our Logetronic copier produces much better copies as it permits variation of the original contrast.

New iodinated contrast materials are constantly being marketed for vascular, renal, and gallbladder studies. When these agents first appear, the literature provides many reports of large series of cases in which the medium was used and gave better visualization with no significant toxicity. Subsequently, there frequently are short reports describing a series of deaths associated

rich the contrast. Because of the frequency of this pattern, our policy has been to continue with a contrast which produces good quality results and not be swayed by the pressures to try a generous sample of a new preparation.

The Food and Drug Administration is becoming more and more effective in removing preparations from the market when a question of safety arises. One product, Orabilex, a cholecystographic agent was withdrawn following reports of deaths thought to be related to this product which fortunately was never used in our department. Recently, tannic acid preparations used in cleansing and barium enemas have come under investigation following reports of a small series of deaths due to liver necrosis which may have been induced by tannic acid.

Kinescopic tape recording of fluoroscopy studies is becoming increasingly more popular particularly for dynamic studies in children since the radiation dose is far less than from cineradiography. Where fine detail is desired, as with the cardiovascular evaluations, cineradiography is superior. Although the main department has not completed taping facilities, these facilities have been available to the heart catheterization laboratory for several months. During a recent study of a heart patient, a technical failure prevented the completion of recording cineradiographically; however, the procedure was being recorded on tape and subsequently could be viewed and evaluated.

Automatic data processing is being utilized with increasing frequency. A pathology index code is being completed by The American College of Pathology and will serve as a foundation for processing radiographic pathology.

New types of X-ray equipment are being presented as well as modifications and improvements of established units. A very interesting new development is a unit imported by Westinghouse which has a 0.1 mm. focal spot and an X-ray source housed in a tubular structure the size of a small finger which may be utilized in proximity to areas to be demonstrated excluding the superimposition of adjacent structures on the study which previously could not be avoided because of the limitation of positioning of the X-ray source. In addition to the very versatile source, the cassettes are flexible so they may be wrapped around a structure recording the various components with minimal obscuration from adjacent structures. The very small focal spot produces exquisite detail.

Other developments in equipment include more utilization of transistorized circuitry which is extremely compact and does not produce heat which deteriorates circuits.

Remote control of equipment has not become as popular as originally predicted. This may be related to the cost but, more significantly, the patient-doctor relationship becomes automated and many radiologists have rejected such change.

A complete diagnostic neuroradiology room is being planned for the main department which will include all the equipment to complete any desired study. At present, the various equipment is in several locations. Two deterring factors have been finding a room sufficiently large for the purpose and obtaining some degree of uniformity on the preferred equipment for various procedures by the neuroradiologists.

The chest X-ray facility for employees adjacent to the EHS Clinic will be completed in the very near future and will save employee time loss as well as increase the yield on annual chest studies because of the convenience.

Consideration of the pros and cons of phasing out the radiology residency and X-ray technician training programs will be pursued. The technician training school no longer serves the purpose for which it was established and the Clinical Center might better be served by qualified staff radiologists in the resident positions for the same or similar financial investment.

General plans for future staffing include the desire to have an expression of a special interest channel for a given area of radiology in addition to being well qualified in all phases of the field. To date we have managed to have the continued availability of the special talents in neuroradiology, cardiovascular radiology, and radioisotopes. In addition to these areas, special qualification in gastrointestinal, pulmonary, bone and joint, genitourinary radiology for any given radiologist would make a significant contribution to the research projects of the Institutes and would be very rewarding to our department. I believe this can be developed within the group as well as taken into consideration when replacing a staff radiologist.

Although much improvement has been realized in the organization of our X-ray museum, much greater effort is planned for this endeavor. The Logetronic unit has been very helpful in enlarging our museum collection. It is planned to microfilm our museum cases for use by the many physicians who need refresher experience in X-ray in preparation for their board examinations in specialities other than radiology. We have permitted them to peruse our museum cases for this purpose; however, the frequent handling of the films is causing some deterioration.

We plan also to begin microfilming employee chest films by converting a photofluorographic machine to a filming unit. There is no immediate plan to dispose of the original films immediately; however, as space becomes more limited, the studies done five years previously on employees who no longer are locally employed could be discarded if the miniature record remains available for possible future reference.

Progress Achieved

There was a slight decrease in all phases of the workload with respect to X-ray examinations except for special procedures. These were increased by 321 studies and represented a very significant investment of time. The need to conduct a constant refresher program for technicians for the cardiovascular and neurosurgical suites in 10A and coverage of the satellite area for gastrointestinal physiology more than balanced the modest decrease in examination workload.

Many structural changes were completed which permitted more efficient utilization of the space in the department and solved specific problems that existed.

Improvements were made in the film library organization which improved efficiency and provided better service for the physicians and patients.

[illegible] was instituted to evaluate the amount of work being done in each [illegible], the amount of time individual studies required, and to record data on problems that were encountered.

A new satellite X-ray area for gastrointestinal physiology was completed and [illegible] for others--employees health and genitourinary surgery--progressed.

Although we lost our neuroradiologist to another institution, we had an available replacement since one of our staff radiologists had had one year of experience in neuroradiology in Sweden. He has taken over this area in the department and has demonstrated superior technical skill and background.

Considerable strides were made in the expansion and development of the radioisotope clinical service. Additional equipment and space materialized and is combined with a very able staff radiologist with an interest in this field resulted in a service of quality. New techniques and one new isotope proved successful and informative.

Four very important pieces of equipment were obtained, namely, the Westinghouse image intensified fluoroscopy unit, a rapid serialographic Schonander biplane 105 film changer, a Packard body scanner, and a Logetronic film duplicating unit.

A full complement of four residents and eight technician students was attained.

Radiologic contributions were made to intramural research programs which were rewarding.

The radiology staff presented a number of lectures and conferences locally and to out-of-state medical groups as well as provided consultation.

Many professional visitors were received and ideas exchanged.

The new surgical wing began operation and the many technical problems were resolved as they presented. Adequate professional and technical service was established.

A standardized chest room was organized which has resulted in better quality films and fewer repeat examinations.

Major Problems Encountered

The October flood constituted our most major negative event requiring considerable ingenuity and a vigorous energy expenditure to restore and preserve the X-ray studies of 8500 patients. Only 10% of the films were marred by residual damage.

Employee turnover presented a problem which appears to be constant. Corrective action cannot be applied since the working environment has not significantly contributed to this mobility of the work force. Two additional employee problems include frequent use of sick leave and the simultaneous pregnancy leave

of six months each for two technicians. Thus hardship conditions resulted for those on duty.

We were fortunatly able to promptly retrieve our radiology residency from a probationary status. Changes in regulations of the American Board of Radiology precipitated an intensive residency inspection drive throughout the country. Two programs in the Washington area were closed. There is some thought that this severe approach is related to the supply and demand of potential residents.

An astounding cost has resulted from a part-time on-the-job-training program for X-ray equipment repair and maintenance for an employee of IED. The solution rests with the establishment of a salary grade at which an experienced full-time man may be hired at half the cost of the present system.

Honors, Awards, and Publications

Twelve papers were authored or co-authored by six staff radiologists.

Honors were received for an exhibit on axial transverse pneumoencephalography at the annual meeting of The American Roentgen Ray Society.

Our first year resident was one of the recipients of a superior service award in April 1963 for his efforts prior to joining our group.

TABLE I

NUMBER OF X-RAY EXAMINATIONS

1/1/62 - 4/30/63 AND 1/1/63 - 4/30/64

JANUARY 1, 1962 - - - - - - - - APRIL 30, 1963	
INSTITUTE	NUMBER OF EXAMINATIONS
NCI	16,156
NHI	9,373
NIAID	3,266
NIAMD	7,577
NIMH	370
NINDB	7,052
NIDR	738
EHS	10,582
TOTAL	55,114

JANUARY 1, 1963 - - - - - - - - APRIL 30, 1964	
INSTITUTE	NUMBER OF EXAMINATIONS
NCI	13,286
NHI	10,183
NIAID	3,293
NIAMD	6,156
NIMH	500
NINDB	7,319
NIDR	619
EHS	10,413
TOTAL	51,769

TABLE II

RADIOACTIVE ISOTOPE PROCEDURES

1/1/62 - 4/30/63 AND 1/1/63 - 4/30/64

JANUARY 1, 1962 - APRIL 30, 1963		JANUARY 1, 1963 - APRIL 30, 1964	
THYROID UPTAKES		THYROID UPTAKES	
THYROID SCANS		THYROID SCANS	
BRAIN SCANS		BRAIN SCANS	
		CISTERNOGRAPHY AND VENTRICULOGRAPHY	
		LIVER SCANS	
		HEART SCANS	
		SPLEEN SCANS	
TOTAL NUMBER OF STUDIES	1,040	TOTAL NUMBER OF STUDIES	974

TABLE III

X-RAY SPECIAL PROCEDURES

1/1/62 - 4/30/63 AND 1/1/63 - 4/30/64

JANUARY 1, 1962 - APRIL 30, 1963	TYPES OF EXAMINATIONS	JANUARY 1, 1963 - APRIL 30, 1964
TOTAL NUMBER OF EXAMINATIONS 1,159	CINERADIOGRAPHY ANGIOCARDIOGRAMS CARDIAC CATHETERIZATIONS AORTOGRAMS - CELIAC LUMBAR ARTERIOGRAMS - FEMORAL RENAL CEREBRAL PHLEBOGRAMS INFERIOR VENACAVOGRAMS BRONCHOGRAMS MYELOGRAMS PNEUMOENCEPHALOGRAMS VENTRICULOGRAMS CYSTOGRAMS RETROPERITONEAL AIR STUDIES SIALOGRAMS HYSTEROSALPINGOGRAMS GYNECOGRAMS SEMINAL VESICULOGRAMS LYMPHANGIOGRAMS ANIMAL STUDIES	TOTAL NUMBER OF EXAMINATIONS 1,480

TABLE IV

SUMMARY OF ACTIVITY

	1/1/62 - 4/30/63	1/1/63 - 4/30/64
TOTAL NUMBERS OF PATIENTS EXAMINED	31,096	29,783
TOTAL NUMBERS OF X-RAY EXAMINATIONS	55,114	51,769
NUMBER OF X-RAY EXAMINATIONS PER PATIENT	1.77	1.73
TOTAL NUMBERS OF RADIOISOTOPE STUDIES	1,040	974
TOTAL NUMBERS OF X-RAY SPECIAL PROCEDURES	1,159	1,480

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

DENTAL DEPARTMENT

CC-36
Serial No.

The responsibility which the Dental Department of the Clinical Center has in supplying examination, diagnosis, consultation and dental treatment to the patients of the Clinical Center, National Institutes of Health, has been performed satisfactorily in the calendar year 1963. In addition, the Department has rendered a more detailed and expanded service to both the in-patients and outpatient of the National Institute of Dental Research who, by nature of their dental illness, are in need of such special consideration. The Clinical Director, NIDR, assumes responsibility for dental research; and the Chief, Dental Department, Clinical Center, has the responsibility for patient care.

Whereas the dental service rendered in many university and research hospitals is considerably different from the routine hospital dental service in certain areas, the operation of the Clinical Center Dental Department is even more unique in many respects. This is because the clinical research programs of the seven Institutes include a particular population of medical and surgical entities, whose dental problems are very much at variance from that seen in the average or even specialty hospital.

In an effort to enhance the total National Institutes of Health research effort, the Dental Department collaborates with many of the categorical Institutes. Continued special attention was given to the patients of the National Cancer Institute, National Heart Institute, and National Institute of Arthritis and Metabolic Diseases. There was an increase in the number of maxillo-facial devices and obturators constructed for patients with cancer. These ingenious prosthetic devices, although very often complicated and time-consuming to produce, are necessary in the post-surgical management of intra-oral and extra-oral head and neck cancer. A number of artificial noses, ears, and eyes of a very high quality, which often defied detection by the critical observer, were produced for the National Cancer Institute patients.

Patients admitted to the National Heart Institute for heart surgery or other cardiovascular problems usually present with major oral problems because of inadequate dental care given in the past to their dental mechanism. Special considerations are

necessary in the performance of dental operation in the patient with hypertension, rheumatic heart disease, pre- and post-care of all cardiac surgery patients.

In cooperation with the Hematology Branch of National Institute of Arthritis and Metabolic Diseases, extensive oral surgical procedures have been performed on the classical hemophiliac patients. The administration of Fraction I (fibrinogen fraction) containing AHG (anti-hemophilic globulin) has been used successfully for extracting teeth in hemophiliacs. In one case 28 teeth extractions, including three impactions, followed by a generalized alveolectomy, were performed in a single operation, without complications. The patient is now wearing satisfactory dentures, without incident.

The Dental Department provides clinical study facilities and assistance for the staff of the National Institute of Dental Research. A large component of senior investigators with ancillary personnel (approximately 27) utilize the Dental Department on a part-time basis. The Dental Department personnel cooperate fully in these research endeavors.

During the latter part of March 1964 and the first two weeks of April, the main dental laboratory was renovated. Using some of the former equipment and cabinets, the laboratory was redesigned (1) to provide more efficient work arrangements for the two full-time dental technicians, (2) to replace obsolete equipment and work patterns, (3) to separate the gold restorative area from the denture acrylic fabrication equipment, and (4) to provide additional and separate bench space for the professional staff. The final result is most gratifying. The dental laboratory is now a modern, bright, and more efficient facility.

The concealed modular dental unit design was completed in room 1B-05 in late 1963. During the limited period of use, it has proved to be flexible for the various types of dental chairside procedures. This design allows more comfort for the chronically ill patient, and for the operator and ancillary personnel; thus improved quality of care is provided.

The Dental Department has performed all types of dental treatment, as shown by the following statistics:

	1961	1962	1963
Admissions to Clinical Center	3,876	3,906	3,860
Examinations	1,540	1,629	1,793
Visits	10,827	14,029	13,187
Treatments	12,150	19,697	28,315

January 1, 1964, through June 30, 1964 (estimated figures from present through June 30, 1964)

Admissions to Clinical Center	1,930 (estimated)
Examinations	1,233
Visits	6,710
Treatments	15,906

Personnel

A. Professional. There were six full-time dentists engaged in the previously described dental activities. Facilities and assistance were provided for 27 NIDR dentists.

B. Administrative. Five full-time employees and one part-time employee were engaged in this activity.

C. Semi-professional and ancillary. One dental assistant was assigned to each dentist. There were three hard-working dental technicians. One nurse, one dental hygienist, and one x-ray technician were on duty the full year. A medical aide was also on full-time duty.

Objectives and Plans for the Future

The objective of the Dental Department, as originally conceived, was to furnish the highest quality dental diagnostic and treatment service to the patients of the Clinical Center. In addition, it was to provide intelligent consultation on dental problems as they relate to the diseases being studied and to provide an evaluation as to what part dentistry plays in the conduct of the individual research projects.

The Department has continued to perform these major functions and has provided, in addition, a valuable morale building and maintenance service not only to ill patients but to the normal volunteer patients as well.

An increasingly large number of visitors from all over the world visited the Dental Department and were escorted on tours by members of the staff.

The following articles by Clinical Center Dental Department officers were published:

Swerdlow, H. Advanced periodontal disease in an adolescent (periodontosis). J. Periodont. 34:533-539, Nov. 1963.

Swerdlow, H., and Stanley, H.R., Jr. An approach to biologic variation in human pulpal studies. J. Pros. Dent. 14:365-371, Mar.-Apr. 1963.

Rowberry, S. Technique for constructing a custom-made mouth protector. Dent. Dig. 69:296-302, July 1963.

Rowberry, S. How to test hemorrhage. Oral Hyg. (Latin-Amer. Edition) 16-21, Jan. 1964.

Swerdlow, H. Roentgencephalometric study of vertical dimension changes. Accepted for publication in J. Pros. Dent.

Abstracts Published:

Swerdlow, H., and Stanley, H.R., Jr. Response of human dental pulp to amalgam restorations. Dent. Abstracts, 8:105, Feb. 1963.

Presentations of lectures, papers, and table clinics included:

Blythe, J.O., Jr. "Maxillo-facial prosthetics"
(1) Baltimore College of Dental Surgery, University of Maryland Seminar, May 1963 (2 presentations), April 1964 (2 presentations).
(2) USPHS Hospital Dental Staff Meeting, USPHS Hospital, Baltimore, Maryland, June 1963.
(3) USPHS Hospital General Staff Meeting, USPHS Hospital, Baltimore, Maryland, March 1964.
(4) Oral Cancer Prevention and Detection Center of St. Francis Hospital, Poughkeepsie, New York, May 1964.

Swerdlow, H. "Vertical dimension changes in natural to immediate dentures," International Association for Dental Research, Pittsburgh, Pa., March 1963.

Swerdlow, H. "Use of corticosteroids in operative dentistry," Postgraduate Clinic, District of Columbia Dental Society, Washington, D.C., March 1964.

Swerdlow, H. "Restorative procedures using parallel pin retention," USPHS Hospital Dental Staff, Baltimore, Md., April 1963.

Swerdlow, H. Participated in the television production entitled "Minimizing pulp trauma in restorative dentistry," sponsored by the Colgate, Palmolive, Peet Co., through the A.D.A. and the Professional Closed Circuit Television, Inc., January 1964.

Rowberry, S. "Dentistry--an aid in identification," USPHS Clinical Society, Gallup, New Mexico, May 1963.

Rowberry, S. "The chronically ill individual as a dental patient," USPHS Clinical Society, Gallup, New Mexico, May 1963.

Rowberry, S. "Powdered gold--its use in dentistry," USPHS Clinical Society, New Orleans, La., April 1964.

Lightbody, P.M. "Functionally generated path technic as used in construction of gold restorations," Postgraduate Clinic, District of Columbia Dental Society, Washington, D.C., March 1963.

January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

CLINICAL PATHOLOGY DEPARTMENT

CC-37
Serial No.

SUMMARY OF ACCOMPLISHMENTS

The annual workload of this Department in 1963 stabilized at approximately 500,000 tests in contrast to the progressive increase experienced in previous years. This was principally caused by necessary and continuing restrictions placed on certain tests and the termination of several hospital surveillance studies. An acute space crowding made these measures mandatory to avoid sacrifice of accuracy and quality control. When 8 recently allocated modules become available for occupancy this space pressure will be partially alleviated and with progress in automation and data processing the future workload capacity will be improved. We have begun "phasing in" some of the tests that were suspended to relieve acute space shortage. A further reflection of the workload stabilization has been a sharp decrease in the technical staff growth rate from 26% to 6%. In spite of this, the laboratory evening coverage is expanding to include an "in-house" technologist throughout the night in Clinical Chemistry. The other two services are covered by "in-house" personnel until 8:00 p.m., and by "on-call" technologists for the rest of the night.

The high level of supervision provided in Clinical Chemistry, Microbiology, Hematology, and the Blood Bank by the Laboratory Chiefs, Dr. Cotlove, Dr. Young, Dr. Brecher, and Dr. Schmidt has encouraged continuing demands for their collaboration in problems of patient care and clinical investigation. Collaborating research continues as a significant part of our contribution to the mission of the Clinical Center. In spite of the administrative demands on the Service Chiefs they have managed to accomplish some independent research in their respective specialties. Significant contributions especially in methodology and consultation, continue to be made by our Visiting Scientists, Dr. Radde, (Clinical Chemistry), Dr. Tanaka, (Hematology,NCI), and Dr. Yokoyama, (Immunohematology, NCI).

A standard work unit was developed based on a thorough analysis of our laboratory operation and was established for effectively measuring workload, automation effects, and relative productivity.

The EAM card system for data processing has proven efficient and economical in Clinical Chemistry, salvaging 40 technical man-hours each day. The Hematology Service was integrated into this system during May. To provide a fully automatic analytic system and expand the data processing capacity, a detailed plan has been developed for incorporating a digital computer into our laboratory operations. Computer specifications were delineated and the

most suitable configuration selected for purchase and installation by February 1965. A 3 unit prototype equipment designed by Airborne Instrument Laboratories for automatic analysis was delivered in February. One unit automatically accessions and loads specimens and another samples the specimen, assays for glucose and urea nitrogen and the third transmits the test result and its identification to the computer. This is already in routine patient care service utilizing manually marked punch cards to conform to our current data processing system. It has proven highly successful in actual operation.

The continuing study on normal individuals has additional valuable information defining normal population ranges of test results and individual differences. Recently, alkaline phosphatase, thymol turbidity, total and direct bilirubin, cephalin flocculation, amylase, and creatinine have been added to the tests included in the normals study.

An "Early Warning System" has been established in all three Services to detect and immediately report any laboratory data which indicate hazard to a patient's life.

PATIENT CARE CONTRIBUTIONS

1. Workload

Year	Total Tests (B.B. not inc'd)	Increase Over Previous Year
1963	525,000	- 5% *
1962	555,000	25%
1961	445,000	13%
1960	399,000	15%
1959	346,000	19%

* The apparent decrease of 5% when corrected for a decrease in the patient census (bed occupancy) becomes an increase of 1%.

The patient care service, as measured by the number of tests performed, was approximately the same in calendar year 1963 as in 1962. This is at variance with the pattern seen in this laboratory and in laboratories throughout the world in recent years. Although there was a decrease in average patient census in 1963 as compared to 1962, the major reasons for the stabilization in work volume were reluctant but necessary and vigorous efforts by this Department to limit certain laboratory requests to the minimum essential for adequate patient care. Individual written and signed justifications for several tests were required and several surveillance programs and studies were terminated. Examples of these "rationing" procedures are the requirements of a full page written justification for protein electrophoresis, serum protein bound iodine, urinary steroids and other 24 hour urine analyses. By conferences with the Clinical Directors and frequent personal contacts with patient care physicians, our staff waged a continuing campaign to limit our laboratory work to an achievable level. A valuable study of the bacteriological changes caused by pre-operative bowel preparation for cancer surgery

was necessarily terminated in mid-study. Bacteriological surveillance of Staphylococcus carriers was discontinued. Thus we succeeded in maintaining a stable workload at the sacrifice of valuable services which must be re-established at the earliest possible date. Such a practice may be justified as a temporary stopgap but is untenable as a policy in modern patient care and clinical research. Partial relief of our space shortage by the acquisition of 4 modules previously occupied by the Commissioned Officers Dental Clinic and 4 modules from Occupational Therapy will permit the reinstitution of a number of procedures on a desirable routine basis. Our progressive program of automation and rapid data processing also will contribute to providing quality controlled laboratory analyses in larger volume.

New Workload Measure

To better estimate the workload of the Clinical Pathology Department by a method that takes into account the vast differences of complexity of tests, of demands on staff time by different tests, and of the effects of automation, our laboratory operations were analyzed and a new system of measurement was devised and instituted by Dr. Douglas Morningstar from our staff and Mr.George Russell of the Management Analysis Branch. Many other systems were reviewed and discarded as too complex, awkward, or meaningless in application. This system employs a time-based standard work unit which measures direct productive, other productive and non-productive time devoted to each test by the technical staff. Since July 1963 the workload in Clinical Pathology has been measured and reported in terms of Work Units (W.U.). Experience to date clearly demonstrates that this work unit is a more realistic measure for evaluating workload and technical productivity. The relative workloads and technical staff requirements of the laboratory services can be realistically compared. Furthermore, this information can be converted to "W.U./tech/day" and "procedures/100 W.U." to express the technologist's individual workload and the efficiency of laboratory operations. Thus, it is a better tool for judging personnel needs and effects of automation than the conventional method of counting tests. A comparison of our former "test" system to our present "work unit" system is made in the following table. The number of test procedures is used in this report for direct comparison with previous years. Next year, the second year of use of the new unit, workload comparisons will be expressed in Work Units.

	1963						1964						
	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	Total
Avge Pt Census	379	368	345	382	387	363	390	395	379	376	376	376	
Total Pt Days	8,338	8,096	6,900	8,785	7,353	7,639	8,580	7,505	8,338	7,948	7,948	7,948	95,378
Equiv.Tech.Days	1,139	1,042	977	1,148	1,107	1,165	1,316	1,138	1,251	1,143	1,143	1,143	13,712
Work Units	74,663	67,209	66,541	73,664	65,267	64,541	76,420	67,570	70,458	69,593	69,593	69,593	835,112
Total Tests	46,958	42,270	41,850	46,330	41,048	40,592	48,063	42,497	44,313	43,769	43,769	43,769	525,228
Work Units/Tech/Day	66	65	68	64	59	55	58	59	56	61	61	61	
Tests/Tech/Day [1]	41	41	43	40	37	35	37	37	35	38	38	38	
Work Units/Pt/Day	9.0	8.3	9.6	8.4	8.9	8.5	8.9	9.0	8.5	8.8	8.8	8.8	
Tests/Pt/Day [1]	5.6	5.2	6.1	5.3	5.6	5.3	5.6	5.7	5.3	5.5	5.5	5.5	
Proc./100 W.U.*	55	57	56	58	59	60	60	61	57	58.1	58.1	58.1	

[1] Tests per technologist per day and tests per patient per day are reported this year only for purposes of comparison with previous reports.

* The term "procedure" is used here rather than "test" because it takes into account the specific operations of each test. For instance, there are several independent operations included in the isolation and identification of the microorganisms of a single bacteriological test of sputum or urine, etc.

2. Consultations

Although the provision of test results for patient care is one of our major concerns, professional consultation on the individual patient is equally important. Indeed, as the field of laboratory medicine continues to expand, this contribution of basic laboratory expertise will be one of our most gratifying and effective activities. Only through automation is it becoming possible to extend professional attention from routine laboratory operation to front-line research-level laboratory consultation. Examples of consultation in the various areas are: Hematology - the diagnostic acumen contributed by Drs. Brecher and Brittin in the differential diagnosis of types of leukemia has aided materially in the effective trial of new drugs specific for a pathological cell type; Clinical Chemistry - the practical knowledge of Dr. Cotlove in acid-base problems and liver functions has assisted greatly in the support of the major surgical procedures performed in the NCI and the NHI, and in chemotherapy of leukemia, and the endocrinologic background of Dr. Radde has been called upon by the Endocrinology Branch of the NCI as well as for patients in other institutes; Microbiology - the knowledge of microbiologic ecology enabled Dr. Young and her staff to alert and consult with patient care physicians in dealing with recent infectious problems such as fungemia, Staphylococcus outbreaks, and gas gangrene infections; and in the Blood Bank - Dr. Schmidt and his staff are constantly providing competent consultation dealing with a vast array of problems inherent in a service that provides whole blood and blood products, especially platelet rich plasma, for the leukemic and surgical patients.

3. Collaborative Contributions

Many contributions to the design as well as the execution of clinical studies in the Institutes were made by our senior staff.

In Hematology, Drs. Kundel and Brecher joined with Dr. Levin of the NCI Leukemia Branch in a morphologic review of all the cases of acute myelogenous leukemia treated at NIH. Their findings indicated that those patients in whom Auer bodies and granules were identified in the marrow leukocytes had a significantly better prognosis. Drs. Bronson and Brecher investigated the problem of bleeding in the postoperative period of heart surgery patients with Dr. Gilbert of the Surgical Branch, NHI. The patients who are maintained for long periods on extracorporeal circulation with heparinized blood were found frequently to have a problem of "heparin rebound" - once thought rare. This may be due to extravascular storage of heparin with a subsequent release into the blood. The great importance of careful laboratory surveillance of these patients during the critical postoperative period has been well borne out by this study.

In Clinical Chemistry, Drs. Cotlove and Bronson are currently collaborating with Dr. Baldwin, NINDB, in a study of chemical changes in the blood, urine and cerebrospinal fluid in response to surgery for a variety of central nervous system lesions. Dr. Cotlove is studying the composition of thoracic duct lymph with Dr. Ketcham, NCI; he and Dr. Butler, NIAMD, determined the toxic effects of Amphotericin B. on patients. He has worked with Dr. Anderson, NHI, on the interpretation of complex changes of acid-base balance

in patients before, during, and after cardiac surgery. The data examined thus far have already disclosed certain characteristic features of physiologic disturbance which is of great importance in proper management of patients undergoing open heart surgery. Dr. Radde and Dr. Ross, NCI, studied electrolyte excretion following alterations in circulating parathyroid hormone levels of patients with gonadal dysgenesis or acromegaly. She has worked with Drs. Gittes and Ketcham, NCI, on the effects of different forms of experimental hyperparathyroidism on calcium and magnesium homeostasis. With Dr. Clendenning, Dr. Radde evaluated renal tubular defects in patients with certain dermatological syndromes by measuring chemical renal clearances.

In Microbiology, Drs. Young and Olch began a joint study with Dr. Ketcham, NCI, on the changes in bacterial and fungal flora in patients scheduled for major abdominal surgery from the time of admission through the operative and postoperative periods. In addition to radical gastro-intestinal bacteriological changes which were caused by "prophylactic" antibiotic therapy, an alarming number of dominating yeast cultures were found. These results contributed directly to the modification of the procedures for preoperative bowel preparation. Antibiotic discs of a new anti-psuedomonas drug have been tested for Dr. Emil Frei, NCI, and these were found to be quite ineffective against that organism, but very effective against Klebsiella. Also, a new drug, Gentamicin, is being evaluated with Dr. Gerald Bodey, NCI.

IMPROVEMENTS IN SERVICE

Although space limitations have prevented the introduction of many new tests desired by the patient care staff, we have made important improvements in methods already in use.

In Clinical Chemistry, lactic acid, blood methyl alcohol, and urine osmolality determinations have been added to the routinely available tests. Modifications of existing tests include an improved Autoanalyzer procedure for the determination of alkaline phosphatase, increasing the number of tests run from 40 to 60 per hour; the inclusion of chlorides in the simultaneous electrolyte battery; the reading of cholesterol determinations by the BBN automatic readout colorimeter (immediately adaptable to computer input); and the design and construction of a sample feeding device for the Zeiss flame photometer which is capable of introducing 300 samples an hour. An "Early Warning System" has been recently established to "flag" any serious abnormal chemical result which could hazard a patient's life. This is telephoned to the patient's physician immediately. For instance, the dramatic finding of a dangerously low blood sugar which was not requested, but discovered during analysis for BUN, enabled prompt treatment and remarkable improvement in the patient's critical condition.

In Hematology, a similar "Early Warning" system was instituted with particular regard to detecting massive intravascular hemolysis. We have developed a method for very rapid estimation of hemoglobinemia which permits immediate diagnosis and continuous monitoring of the progress of the patient. An illustration of the life saving importante of close coordination of the Clinical Pathology Services was the prompt correlation of an unexpected

finding of hemolysis (hematology) in a patient with a bacteremia (microbiology) which indicated a grave gas gangrene infection. This was diagnosed and treatment started before the onset of clinical symptoms. In the past year, radioisotope studies have become part of the routine patient care services. These include the use of radioactive iron for iron absorption study, radioactive cobalt for Schilling tests, and radioactive chromium for red blood cell survival measurements. With Dr. Howard Andrews and use of the whole body counter in his department, we have started measurements of iron and B_{12} absorption. This has been shown to have distinct advantages over the conventional methods of isotope assay. Chromatographic column separation of A_2 hemoglobin permits sharper differentiation of A_2 from A hemoglobin, which was often unsatisfactory with the previously used starch block technique. This test is frequently requested to rule out Thalassemia Minor as a cause of mild anemias. The presently used method of measuring iron binding capacity (IBC) of the serum using dipyridil is being replaced by one using nitroso-R after precipitation of free iron by magnesium carbonate (Ness). This will greatly simplify the test and increase its precision.

In Microbiology, there has been an intensification of the early warning principle. Fluorescent antibody methods for rapid identification of bacteria and fungi are being established. They will include indirect techniques which can then be applied to all of the bacterial anti-sera which are or will become available. Dr. Ryschenkow is developing rapid fermentation techniques and millipore filtration concentration and culture methods to provide more rapid diagnosis in cases of septicemia or fungemia. As a further rapid service to the patient's physician, urine cultures are read early every morning and all specimens with a count exceeding 10,000 microorganisms per ml. are immediately reported by telephone. Also, rapid methods for antibiotic sensitivity determinations are being instituted. A night technologist is now available in Microbiology, and the routine reading of blood cultures in the evenings and on Sundays has been established.

DEVELOPMENTAL RESEARCH

Data processing and automation of analytical procedures have greatly improved our understanding of the details of laboratory operation so necessary to development of further efficiency and incorporation of a computer. Our EAM card system has been in successful operation and thoroughly evaluated for 2 years in Clinical Chemistry. The system utilizes IBM punch cards and sorting, reproducing, collating, key punching and accounting equipment. Requests are made on mark-sense cards from which result cards are reproduced. Technologists mark analytical results on these mark-sense result cards which are sorted, merged with the "master" request cards and generate the final printed reports for each patient. This system is being expanded currently to handle hematological data. Data processing for the Blood Bank will be included by the first quarter of the next fiscal year (FY '65). To avoid slowing the Clinical Chemistry processing, a second sorter was found necessary to handle Hematology and Blood Bank cards.

In January 1964, the Airborne Instrument Laboratories delivered a prototype automatic system for blood sugar and urea nitrogen assay. This consists of

an automatic specimen accessioning, numbering and loading unit, special 5 tube sample racks, a sampling unit which delivers aliquots of each specimen to the autoanalyzers; and a scanning multiplexer which transmits the test result, its identification, and test number to the computer. For operational evaluation, duplicate samples from the daily patient work were assayed on the new instruments for glucose and urea nitrogen. The evaluation proved highly successful and the new equipment was integrated into the patient care routine during April.

In the X-ray Spectrograph laboratory, Dr. Morningstar has developed methods for precise determinations of hemoglobin iron in microsamples of whole blood. With this technique he established for the first time the millimolar extinction coefficient of cyanmethemoglobin as 11.0 by direct physical measurement of the iron in hemoglobin. This value is in agreement with several workers in Europ, but at variance with 11.5 as established in the United States. The X-ray Spectrograph has been applied to determine calcium in 30 microliter samples of serum and iron in the urine of patients being treated for iron overload syndromes. Other methods for the assay of urinary sulfate and plasma fibrinogen are being devised.

In Hematology, work is continuing on platelet enumeration with the Coulter Counter, and several published methods are being evaluated. The Coulter Counter is also being used extensively in the differential sizing of red blood cells. It is now possible to determine the relative size of red blood cells at the top and bottom of a centrifuged column; thus, size can be related to density. This new dimension has been of great value in diagnosing and evaluating treatment in various types of anemias. With the competent work of Dr. Tanaka, the capabilities of the electron microscope are being developed further in the diagnosis of leukemia, pre-leukemic states, and anemias.

In Microbiology, the capacity for making immunologic diagnoses has greatly expanded. An impressive number of anti-sera have been obtained to broaden bacteriological identification. The fluorescent antibody is being implemented and complement fixation tests are being initiated for the diagnosis of fungus infections. Dr. Wertz has begun to apply automation in this field. It is possible to measure rapidly and automatically the CO_2 produced by small numbers of micro-organisms with the autoanalyzer. It appears feasible to apply this method to rapid antibiotic sensitivity testing and microbiologic assays such as serum folic acid, folinic acid, and vitamin B_{12}.

PERSONNEL

1. Professional Staff

Dr. Viola Mae Young, Chief of the Microbiology Service, was appointed Professorial Lecturer at Georgetown University in March 1964. Dr. Geoffrey Brittin returned from the University of Minnesota in July 1964, and accepted appointment as assistant to Dr. Brecher.

Dr. Leo von Euler was appointed in Clinical Chemistry as an assistant to

Dr. Cotlove for the current year and will transfer to the residency training program on July 1. Similarly, Dr. Douglas Morningstar, who assisted Dr. Williams and was in charge of the X-ray Spectrographic Laboratory for one and one-half years, will transfer to the residency program in July. Drs. John Korzis, Peter Olch, and Richard Wertz will complete their clinical pathology training on June 30. Dr. Korzis will move to the Pathology Department of the Down State Medical Center of New York. Dr. Olch during the past year was invited to give lectures to the history of medicine societies of the Cedars of Lebanon Hospital, Los Angeles, and Vanderbilt University, Nashville, Tennessee. He has accepted appointment as Special Assistant to the Director of the National Library of Medicine, starting July 1. Dr. Wertz will assist Dr. Williams in ultraviolet microscopy for two months and then go abroad to take further training in research at the Centre National de Transfusion Sanguine under Dr. Marcel Bessis. Dr. William Bronson continues as a third year resident, and Drs. Brian Bull, William Kirkham, Joseph Sobota, and Paul Wertlake continue as second year residents. Dr. George Douglas and Dr. Nicholas Pappas also will begin residency training in clinical pathology on July 1, 1964.

2. Visiting Scientists

Dr. Yasakasu Tanaka has continued his important contributions in electron microscopic studies of siderachrestic anemia, inclusion body anemias, and leukemia. This work has been supported by the Diagnostic Research Branch,NCI. Dr. Mitsu Yokoyama joined the Blood Bank staff and has applied immunochemical methods to transfusion problems. This has been supported by the Diagnostic Research Branch, NCI.

Dr. Ingeborg Radde, Chemical Pathologist and Endocrinologist, has continued her valuable participation in clinical pathology research, resident instruction, and has provided endocrine consultative services to the patient care physicians.

3. Staffing

There still is urgent need for personnel to work evening and night shifts. During this year we have employed technologists who cover all our services during the evening hours until 9:00 and midnight. In May a technologist was appointed in Chemistry from midnight until 8:00 a.m. The remaining services were covered by "on-call" personnel. As soon as possible, all services will be covered by "in-house" night technologists. Our goal is to provide necessary patient care laboratory services all-night and weekends. On July 1, 1963, there were 67 technical personnel on board and on March 31, 1964, there were 71. This is a net increase of 6%. Compared to the increase of 14% during the previous 12 months this represents a sharp decrease in the rate of technical staff growth.

Twenty-one technologists (31% of our service technical staff) transferred or resigned. The reasons were: transferred to better positions, 6; resigned for family reasons, 12; and for further education, 3. This is a significant increase of attrition rate compared to the previous two years: 25% in 1962

and 26% in 1963. During the 15-month period, only 25 new technologists were recruited to replace the 21.

4. Training

The residency training program has suffered progressively because of lack of space. The residents have been placed at temporary desks pressed into secretaries' or Laboratory Chiefs' offices. The acquisition of rooms 4D-43 to 49 and an area on the first floor permitted assignment of a module or half module in each Laboratory Service to residents for their service work and study.

Despite crowding, we have retained one module as a conference classroom to conduct an active residency and technologist teaching program. This includes Laboratory Rounds twice each week and luncheon conferences with invited guest speakers. There are weekly teaching sessions by the Laboratory Chiefs, weekly seminars on data processing problems, and periodic instrumentation seminars.

Facilities have been instituted within the Microbiology Service to familiarize the residents with modern techniques applicable to PPLO and virus diagnosis. These techniques include tissue culture cytopathology, hemagglutination, and various immunological methods such as micro-complement fixation, hemagglutination inhibition, and viral neutralization. Also, advanced methods applicable to automation are being investigated in this area. The Clinical Pathology Department participated in the Tutorial Program of Continuing Education of the American Society of Clinical Pathologists. The three tutorials offered this past year were in bacteriophage typing of Staphylococci, the applications of phase microscopy to hematology, and the preparation and use of blood components.

In the several Clinical Pathology Services the resident and senior staff members conduct weekly classes for the technologists and lecture on a specialized subject to advance their training. Every other week there is a meeting of the entire departmental staff during which one of the patient care physicians is invited to describe his clinical research problems and relate them to the clinical laboratory. This continues to maintain the motivation and interest of technologists which is so necessary for the most effective service.

The staff is encouraged to become better trained in their subspecialties. All of the residents have completed the radioisotope course offered by Radiation Safety Branch, as well as the equally superb course in parasitology under Dr. Deaner Lawless of the NIAID. Tuition and text costs were provided for the following staff for special courses:

Name	Grade	Courses	School
Hiroshi Nishi	GS-12	Introduction to Experimental Statistics	NIH
Herbert D. Hochstein	GS-11	#626 Parasitic Protozone	Catholic U.

Anne Jennings	GS- 9	Zoology	NIH
Louis Bourgeois	GS- 9	General Physiology Course	Catholic U.
L. Thomas Byrd	GS- 9	Introduction to Experimental Statistics	
Marcia Lee	GS- 9	Microbiology 101	Univ. of Md.
		Organic Chemistry	American U.
Jean Epley	GS- 9	Introduction to Experimental Statistics	NIH
Jane Berlin	GS- 9	Introduction to Immunology	NIH
James Willett	GS- 7	Introductory Virology	NIH
Arlene Yeterian	GS- 7	Advanced Bacteriology	NIH
		Biochemical Genetics	NIH
Judith Freilich	GS- 7	Introduction to Immunology	NIH
Clinton Thompson	GS- 7	Introductory Biochemistry	NIH
Agatha Jackson	GS- 7	" "	NIH
Maureen Canick	GS- 7	Biochemical Genetics	NIH
Kathleen I. Dahle	GS- 7	Principles of Genetics	NIH
Barbara Plocinik	GS- 5	Introduction to Immunology	NIH
Cynthia O'Connor	GS- 7	Introductory & General Bacteriology	NIH
Martha Ollivier	GS- 7	Introductory Biochemistry	NIH
Dr. Jack Lasersohn	CO	Immunochemistry	NIH
Dr. Douglas Morningstar	CO	Immunochemistry	NIH
Dr. Harvey Cooper	CO	Correlations between Int. Medicine & Basic Sciences	NIH
Dr. Harvey Alter	CO	" " "	NIH
		Principles of Genetics	NIH
Dr. Richard Wertz	CO	Introductory Virology	NIH
Dr. William Bronson	CO	Correlation between Int. Medicine & Basic Sciences	NIH
Dr. Joseph Sobota	CO	Biophysics & Introduction to Immunology	NIH
Dr. Nicholas Pappas	CO	Introduction to Immunology	NIH
		Principles of Genetics	NIH
Dr. Brian S. Bull	CO	Numerical Analysis	NIH
Dr. William Kirkham	CO	Correlations between In. Medicine & Basic Sciences	NIH
Dr. Douglas Morningstar	CO	Clinical Bacteriology	NIH
Dr. Edward Filmanowicz	CO	Immunology & Immunochemistry Genetics	NIH
Dr. Leo von Euler	CO	Basic Enzymology & Biological Energetics	NIH

SPECIAL PROBLEMS

The major problem this past year was the unfortunate necessity of severely restricting the requests for a wide variety of laboratory tests. Utilizing various measures already cited, the annual workload was stabilized to the volume of the 1962 workload. This curtailment was necessitated by increasingly serious space shortage. The recent acquisition of new space partially relieves this pressure and several tests are currently being reinstituted in our department.

The acquisition of the 8 new modules will allow the Laboratory Chiefs to have private offices for the first time. This also will provide a large double module to house the complete data processing equipment including the computer. Some resident desk and bench space will become available. The "remote" areas from the main department will house portions of the laboratory that can best function without continuous support and cross reference to the remainder of the department.

There still is a great need for professional additions in the Clinical Pathology Department. Particularly needed are: an experienced clinical pathologist-administrator to serve as a deputy chief of the Department; another biochemist at the doctorate level, a bacteriologist, and an immunohematologist (doctorate). These appointments will free the Service Chiefs of some of their day-to-day administrative and technical burdens.

Expansion of the residency program must continue its wide scope. The application of chemistry, physics, and basic biology to laboratory medicine is now so complex that the present two-year training is inadequate to provide sufficient experience in one of the subspecialties of clinical pathology. Consequently, a mandatory three-year residency program in this department is projected. The demand from medical schools and larger institutions for clinical pathologists trained in our department is growing rapidly.

FUTURE PLANS

To provide an adequate capacity for data handling and to use the automatic analytical instruments to full advantage, the present punch card system will be replaced with a digital computer. This will perform the tasks of automatic acquisition of raw assay data directly from the analytical instruments and computer results, print-out, patient daily reports, and laboratory data summaries. The computer also will print daily control lists, work sheets and result cards to control laboratory operations. It will eliminate slow and repetitious paper work which is subject to many human errors. The computer will provide storage of all laboratory data in a file immediately available at any time for tabulation of a patient summary, and for later retrieval and correlation in research studies. Periodic printing of patient summaries will replace voluminous accumulations of laboratory slips in medical charts. The appropriate computer also will provide for utilizing high speed mathematical calculations of biochemical conditions important in emergency patient care situations such as shock, postoperative physiological support, etc. Ultimately, the computer will increase the speed of some analyses 3-5 fold, facilitate further automation and reduce the cost per test.

The computer will be delivered with attached data acquisition equipment and program software during February 1965. Debugging of programs and operations should be completed by April when all data processing for Clinical Chemistry, Hematology and the Blood Bank will be handled by the new system. During the last quarter of fiscal '65 programming of Microbiology will be started.

Developments in automation will increase in Hematology and the Blood Bank.

For Clinical Chemistry further development of computer programming, multiplexer on-line data acquisition equipment and another accessioning loader have been contracted. Although the recent developments are more extensive than anything previously attempted in the laboratory, there are still many challenging problems and the opportunities for improvement in patient care have been barely touched. Although there has been much interest and work in other centers on individual automatic analytical instruments, ours is the first effort for an overall system to automatically process specimens from receipt to final report, storing the data for later retrieval and use in further exploration of human disease.

It is necessary for the professional and technical staff to learn the basic principles of the computer operation to enable us to most effectively use the system in our service and research. One of our residents, Dr. Sobota, who received some preliminary computer training in Tulane University, has participated in our planning and development. He is interested in becoming expert in this new area of laboratory medicine as an adjunct to his chief scientific interest in microbiology. He will continue on our staff and later be placed in charge of the departmental data processing activities.

A further challenging opportunity which the computer will make available is the capability of performing high-speed calculations which could permit the rapid assessment of critically ill patients. Complex simulated programs of this type have been under development by groups at UCLA, University of California, and the RAND Corporation. Similar programs, perhaps in abbreviated version, could be employed to provide hour-to-hour control of complex clinical problems and thereby provide a new and powerful tool for more comprehensive emergency patient care.

The development of ultra-rapid methods for microbiological identifications by the fluorescent antibody technique will continue. It is very necessary to achieve answers to problems of serious infection much more rapidly than is now customary. The application of automation to bacterial identification and antibiotic sensitivity has already become feasible, and its incorporation in routine microbiology should be feasible within a few more months.

The use of an electronic particle counter in the rapid estimation and bacterial numbers in urine will be evaluated.

Our study of ranges of chemical and hematological tests in individual normal subjects continues to reveal a much smaller and stable range for the individual than for the normal population. This evidence promises to be of importance in preventive medicine but requires continuing surveillance of each person's chemical and hematological pattern correlated with a physical, X-ray and electrocardiographic examination at regular intervals (6 months to 1 year). A program of Health Conservation for career employees of NIH is highly desirable especially to preserve the health and exercise "preventive maintenance" of the physiology of our most effective and valuable staff.

Some other departments in the Federal Government have established programs of periodic health examinations for their executive staffs. If any group in the government should lead in this profitable effort, it is the USPHS and

particularly NIH. Therefore, as soon as automation sufficiently increases our capacity we should start a program of Health Conservation by periodic physical and laboratory examinations and surveillance of each participant's individual pattern, paying particular attention to changes toward the abnormal which may warn of beginning chronic disease. At first only small selected groups could be accommodated, but as automation permits and a night shift of routine analyses develop, the program could be gradually extended to all long-term career employees.

The qualitative excellence of our resident training program in Clinical Pathology is producing a rapidly mounting demand for training here and for our graduates in academic and institutional appointments. The volume and nature of our work could easily provide training opportunities for 3 or 4 more residents and 4 postgraduate fellows for advanced clinical pathology and specialization in Clinical Chemistry, Hematology, Microbiology, Immunohematology and Transfusions and Laboratory Administration. Initiation of this highly desirable addition to our training activities awaits sufficient space and the necessary additional personnel positions.

Another area in which we can and should exercise our national leadership is in conducting an annual one-week Clinical Pathology Refresher Course of lectures and demonstrations. With the assistance of lectures and demonstrations by some of our colleagues in the Institutes we could conduct a superb refresher course in advances in Clinical Pathology. This would match the similar series of yearly AFIP Lectures in Pathology which attracts pathologists from all over the world.

CLINICAL CENTER BLOOD BANK

The Blood Bank under Dr. Paul J. Schmidt is one of the four professional services of the Clinical Pathology Department. Because of the radical difference in type of expenditures, it is operated under a separate budget and this report is therefore made as an addendum to the Department report.

SUMMARY OF ACCOMPLISHMENTS

Patient care service was provided in a quantity comparable to that of calender year 1962 with continued high quality of service. The move into new quarters was achieved with no break in service. The additional space acquired was assigned to use in an intensive program of blood procurement. Within a few short months a volunteer donor program has been brought to a level of 250 donations per month. Laboratory services had frequent peaks in demand when the staff worked long hours at maximal output. Professional collaboration in problems in clinical research has continued to be demanding of time and fruitful of effort with significant findings in the relationship of the blood groups and disease as well as in the chemistry and physiology of the immune response. Developmental research has been continued in the improvement of technical methods, and an automated blood grouping apparatus has been produced and is being adapted for routine use.

PATIENT CARE CONTRIBUTIONS

1. Work Volume

The work output is measurable under two overlapping parameters: (a) Number of Transfusions, which is a measure of the overall effort of both the laboratory and nursing staff; and (b) Work Units which measure the activity of the laboratory technical staff only.

(a) Number of Transfusions

There has been a decline in total usage of blood and blood products:

	July-Dec. 1962	Jan.-June 1963	July-Dec. 1963	Jan.-June 1964
Whole blood	2855	2614	2513	2974
Blood fractions	4608	3994	3695	3258
Total	7463	6608	6208	6232

This represents a reduction in use of blood fractions but not of whole blood. Most of this reduction reflects a decreased need by the National Cancer Institute for platelet and white cell transfusions. As an illustration, during the first three months of 1963, 1736 of these special products were transfused by NCI but there were only 1251 during the first three months of 1964 -- a 28% reduction. Unfortunately this does not mean less

work for the staff since the reduction has been in platelet material for transfusion which was being obtained preprocessed and required little technical work at NIH before transfusion. The parallel increase in usage of whole blood and the procurement of whole blood in increased quantity from walking donors actually resulted in more work for the laboratory technical staff. This is shown in the category of Work Units.

(b) Work Units

An illustration of the effect of the whole blood transfusion output which far outweighs the platelet effect on technologist workload is shown in the following figures:

	Total Transfusions	Platelets	Whole Blood	Work Units
January 1964	1093	569	437	8514
February 1964	1019	417	510	9852

The workload per technologist went as high as 81 SWU per day in February 1964, although during that month only 365 platelet transfusions were given. Another factor which has a great effect on the work output of the staff is the effort being made to obtain more and more of the blood for transfusion from known local donors rather than by purchasing preprocessed blood. This enables us to supply fresher blood and to use donors who are known not to transmit hepatitis, but requires much more laboratory work per transfusion.

2. Collaborative Contributions

Several complex antibody problems were solved by the professional staff permitting the transfusion of a number of National Heart Institute and National Cancer Institute patients immunized by prior transfusion elsewhere. Consultation and service are supplied to the DBS extramural program of licensing and standardization.

A new approach to transfusion therapy was introduced by Dr. Paul J. Schmid with the use of injection of red cell ghosts (stroma). A NHI patient with an antibody to the I blood factor required 30 transfusions of I negative blood. Since there were not 30 such donors known in the whole world it was decided to bind this antibody in vivo with I positive stroma and proceed with the use of I positive blood. The approach was completely successful and opens up new possibilities in the "transfusion of the untransfusable."

The first direct correlation between a rare disease and a rare blood group has been made. It has been discovered in the Blood Bank that almost a third of patients with leukemia are I negative whereas the incidence of I negatives in the general population is less than one in a thousand. This may be due to a blocking (coating) of their cells with particulate matter resembling the virus-like Eaton agent.

CLINICAL CENTER BLOOD BANK
WORKLOAD TABULATION

1963	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Transfusions												
Whole Blood	638	326	518	339	316	477	566	416	357	417	377	400
Blood Fractions	815	760	703	569	607	540	591	424	551	631	665	830
Total	1453	1086	1221	908	923	1017	1137	843	908	1048	1042	1230
Tests	10564	7276	7400	6073	6302	6997	7704	6237	7061	No longer tabulated		
Work Units	12128	8353	8353	7128	7192	7812	8491	7622	8201	9619	8866	10970
WU/tech/day		Not tabulated					77	67	60	60	69	72

1964	Jan.	Feb.	Mar.	Apr.*	May*	June*
Transfusions						
Whole Blood	437	540	510	496	496	496
Blood Fractions	656	464	509	543	543	543
Total	1093	1004	1019	1039	1039	1039
Tests		No longer tabulated				
Work Units	8514	10041	9852	9469	9469	9469
WU/tech/day	63	81	59	68	68	68

Totals	Calendar 1963	FY' 64*
Transfusions		
Whole Blood	5127	5487
Blood Fractions	7689	6953
Total	12816	12440
Work Units	104,735	110,583
WU/tech/day		68 (mean)

Note: Test and work unit data refer to laboratory activities of technical staff only and exclude nursing staff

*Projected

This finding can be of basic importance to the studies of neoplastic diseases.

Several cases of change of blood group have been studied closely with NCI. These have followed a change in disease state in leukemia or a graft of donor hematopoietic tissue.

A standardized transfusable platelet product was developed in collaboration with NCI and the Research Laboratories of the National Red Cross, giving reproducible results for dosage studies.

IMPROVEMENTS IN SERVICE

Donor Recruitment

The donor recruitment agreement with the American National Red Cross was successfully renegotiated. Under the new terms all NIH employees and their dependents can obtain all their blood needs at any hospital in the country that accepts Red Cross blood. In exchange for this, NIH employees must donate 2,000 pints of blood per year. Despite the fact that the program had to be built up from a level of only 10 to 20 donors a month, it will reach the 2,000 goal in its first year of operation. Use of these walking donors permits the preselection of fresh donors for problem cases, and hopefully will permit screening out carriers of hepatitis. In cooperation with DBS, NIH employee donors are being typed for their blood subgroups. The information is made available to donors and is also used in locating the rarer donors.

Hours of Service

Weekday hours of service were extended to 10 p.m. With the presence of a clinical pathology resident in the hospital, this represents excellent availability of services to patient care staff.

Transfusion Reactions

Reactions to transfusions have been monitored closely by the Blood Bank medical staff in an effort to get more information on the true incidence and importance of adverse responses. As a result of these studies a unique C^W antibody was found which acts only on enzyme treated cells.

DEVELOPMENTAL RESEARCH

The basis for most immunohematological tests and their application in predicting transfusions and transplantation response is a chemical one. With this in mind a program in immunochemistry was begun with Dr. Mitsuo Yokoyama, a Visiting Scientist assigned by NCI. The sera of several patients with an abnormal antibody response to human antigens was fractionated and the activity described. Investigation was made of serial blood samples obtained during induction and rejection of a hematopoietic graft and the rejection found

to be due to an immune response. The unique finding of I negative red cells in patients with malignant disease was shown to be due to a substance coating these cells which can be eluted and used to block the reaction with normal cells.

A multichannel apparatus for automated blood grouping was developed by Technicon Instruments Corporation under research contract. This machine will enable us to continue the work in mechanical quantitation of agglutination tests which will lead to a usable blood grouping system. The machine was delivered March 31, 1964, and our first approach in increasing its sensitivity has been highly successful. We have been able to identify A_x blood using the apparatus. This blood was from a donor who was misgrouped in error by several blood banks several years ago with a resultant hemolytic transfusion reaction. Many technical modifications remain to be made before the apparatus can be applied to routine blood bank use. After these are made, the machine must be adapted to an accessioning system and to an output which can be handled by computer. Since the majority of accidents in blood banking are due to clerical error, the real criteria of readiness for use of the machine in patient care work will be the development of a system for handling and integrating results with complete accuracy from multiple data channels.

Much conflicting information is available in the literature on the incidence and prophylaxis of Homologous Serum Jaundice. A careful retrospective study was made in a possible high incidence group of recipients, patients undergoing extracorporeal circulation (heart pump). Dr. Paul V. Holland was able to get an over 90% followup of these patients who had received over 20 pints of blood, each of which represented a possible exposure to hepatitis. The incidence of the disease in 200 patients was found to be 12%. This is a high figure and a program of study of the prophylactic use of gamma globulin has been instituted. With these high current attack rates this study will give definitive information on the value of prophylactic gamma globulin. This study is coordinated with the interests of DBS, the NRC and the CDC.

PERSONNEL ADMINISTRATION

Dr. Paul J. Schmidt, Chief of the Blood Bank Service was promoted to Medical Director in April 1964. Dr. N. John Pappas and Dr. Paul V. Holland joined the staff in July 1963. Dr. Pappas will enter the residency training program in July 1964 and will be replaced by Dr. Marc E. Weksler. Dr. Harvey J.Alter left June 5, 1964, to complete residency training in medicine at the University of Washington in Seattle.

The professional staff has facilities to work on a limited number of major patient care and developmental research problems at one time. As a result, basic findings which have major clinical significance are often delayed in their application. An attempt was made to begin such a program with the support of Dr. Mitsuo Yokoyama, a Visiting Scientist, by the NCI. This relationship was extremely fruitful but was limited to FY' 64 because of an Institute need for application of their personnel to research problems specific to their program. Dr. Yokoyama will return to Japan. Many of the patients treated at NIH have diseases of an immunologic nature. This selected

hospital population includes patients with lupus, auto-immune anemia and purpura, lymphoma, and leukemia. There are patients who are receiving transplants of hematopoietic tissue and attempts will be made to transplant other organs. All of these clinical research areas are serviced by the Blood Bank. In addition there are multitransfused patients for reoperation and patients with grafted red cell populations. Over the years, Dr. Paul Schmidt has supplied the needed continuity to the program in immunohematology but the extent of the service requested requires that he have a trained assistant at the doctoral level for this purpose. The unique finding of the first correlation between a rare blood group antibody and a rare disease, the I blood group, is an illustration of the type of service and consultation in immunohematology which can be given. It is imperative that the program be made independent of the needs of any one Institute.

Recognition of the unique activities of the Blood Bank nursing staff still awaits recognition in a new grade structure. We have been advised to wait for new qualification and classification standards for nursing positions still expected in FY' 64. Without action in this vital area it will be difficult to retain a competent nursing staff.

The Blood Bank was directed to extend its facilities for the study of the best manner of fiscal operation throughout the entire period covered by this report. This has created the need for advanced management of transfusion and financial records. With its separate budget, the Blood Bank operates administratively as a Clinical Center Department and it will be necessary to recognize this in the grade structure of clerical personnel. A major effort has been successfully completed with the microfilming of some 160,000 record items relating to donors and disposal of the original records. This included the Blood Record Card, Form PHS 2020-1 (years 1954 through 1963); series A-Z of all donor consent cards, Form PHS 2020-2 on blood collected at Merck, Sharpe and Dohme, a source no longer used; and series A-Z of all blood and plasma container labels PHS Form 2020-3 (1960 through 1963).

A data recovery system (Termatrex) has been acquired which will permit immediate location by complete blood type and donor availability of NIH employees who have volunteered to be blood donors.

FUTURE PLANS

It still is the pressing duty of this Service to provide research quality service to the clinical research program. Administrative support has made possible a unique, clinically-oriented service which is engaged in teaching and developmental research as continuing stimuli to its service function.

The application of automation and data processing to blood grouping; pursuit of unique findings in blood groups and disease; continued improvement of methodology in blood procurement, preservation and test procedures; and use of data retrieval in donor location all have high priorities in future planning. The clinical usefulness of the transfusion of red cell stroma will require further work in animals. In cooperation with the

American Association of Blood Banks and the American Society of Clinical Pathologists a program will be started for training and certification of technologists as Specialists in Blood Banking. The Blood Bank cannot refuse or ration blood for transfusion but must meet all requests. At the same time it has complete control over the kinds of laboratory tests it will perform in order to meet this obligation. The continuing unparalleled record for safety reflects the desire of the staff to perform this role with the resources available.

AWARDS

Dr. George Z. Williams, Department of Health, Education, and Welfare Meritorious Service Award.

Mr. Herbert D. Hochstein, NIH Superior Service Award.

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January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

REHABILITATION DEPARTMENT

CC-38
Serial No.

During the period January 1, 1963, through June 30, 1964, as in previous years, the Rehabilitation Department continued to carry out its basic function of patient treatment, using recognized, effective measures of physical, occupational, and speech therapy. Again, a large number and wide variety of tests and measurements were carried out for Institute physicians primarily for evaluation of functional ability and progress, but also in connection with diagnosis and determination of effectiveness of drug and other therapy.

The numerous specific services provided by the Department are listed below:

Physical Therapy Service:

1. Tests and measurements:
   Manual muscle evaluation
   Joint range of motion measurements
   Routine electrodiagnostic testing, including chronaxie measurements and strength-duration curves
   Self-care evaluation (Activities of Daily Living)
   Vital capacity determinations
   Pulmonary function studies (Collins Respirometer)
   Timed vital capacity determinations
2. Heat, including:
   Superficial -- hot packs, infrared, paraffin bath, whirlpool
   Deep -- shortwave diathermy, microwave, ultrasound
   General body heat -- Hubbard tank, Moistaire cabinet
3. Therapeutic exercise:
   General exercise -- passive, active assistive, and resistive
   Muscle re-education
   Ambulation training
   Pre- and postoperative thoracic surgery program
   Pre-prosthetic and prosthetic training
   Training in self-care activities
   Breathing exercises and postural drainage instruction
4. Miscellaneous:
   General and local application of ultraviolet light
   Cervical traction
   Application of splints and casts to maintain joint in good anatomical and functional position

Instruction to patients and family in home care program (application of heat, exercise, and use of self-care aids)
Fitting and dispensing canes and crutches
Prescription and procurement of corrective shoes, braces, corsets, and splints

Occupational Therapy Service:

1. Physical and functional restoration:
   Maintain or regain joint range of motion
   Increase muscle strength
   Improve coordination
   Develop work tolerance
   Train in activities of daily living
   Train in development of substitute skills (visual loss)
   Make splints and provide self-care aids
2. Testing and evaluation:
   Activities of daily living, including self-care and homemaking evaluation
   Record patient's behavior patterns for use in evaluation of patient's reactions in specific research studies
   Pre- and Postoperative performance tests of stereotaxic patients
3. Psychological adjustment:
   Substitute constructive interests for the insecurity and anxiety which may develop during research studies
   Provide normal developmental learning experiences for children
   Promote relaxation and acceptance of bed rest
   Aid in resocialization
4. Psychiatric adjustment:
   Provide activities in relation to needs of research studies and report observations of patient's behavior
   Aid patient in making acceptable social adjustment
   Aid patient in preparing for community living and carrying home responsibilities
   Place patient in industrial therapy program as a step toward post-hospital employment
5. Prevocational exploration:
   Explore skills, interests and work habits
   Increase work tolerance
   Maintain special skills required by patient's job
   Make recommendations on patient's performance and aptitudes for use in vocational planning

Speech Therapy Service:

1. Speech production:
   Dysarthria, dysphonia, speech disorders related to neuromuscular disease, post-laryngectomy, functional articulation problems
2. Language:
   Delayed speech, aphasia (including related reading and writing disabilities)
3. Speech reception:
   Hearing loss

Office of Chief:

1. Electromyography
2. Conduction velocity of motor nerves
3. Repetitive stimulation of peripheral nerves

Special Programs:

The special programs which were continued into the period January 1, 1963, through June 30, 1964, include: 1) Weekly measurements of joint range of motion and determination of joint range percentage deficits for rheumatoid arthritis patients on drug studies. 2) Pre- and postoperative evaluation and treatment of heart surgery patients. These patients are referred for orientation preoperatively and are seen again postoperatively to prevent joint range-of-motion losses and to help them achieve normal functional capacity. 3) Pre- and postoperative evaluation of patients with neurologic disorders who are being considered for operative procedures. The evaluations are concerned with functional activities and capacities, and are submitted to the neurosurgical staff as an aid in final evaluation of surgical results. 4) Treatment of patients with cystic fibrosis, using breathing exercises and postural drainage technics. Added to this program is the evaluation of pulmonary function with use of the Collins respirometer. This includes determination of resting minute volume and tidal volume; timed vital capacity; 1 and 2-stage vital capacity; and maximum breathing capacity. Instruction of patients and parents is emphasized as part of a home program. 5) Evaluation of the use of plaster casts and splints in the treatment of patients with rheumatoid arthritis. Review of data covering 6 years' experience, through June 30, 1964, reveals that a total of 1,028 casts or splints have been applied. Casting has been most effective in the correction of knee flexion contractures, and the relief of pain in the arthritic hand and wrist.

A new special program was begun in July 1963 for patients with ALS. Efficacy of drug therapy for such patients is being evaluated by NINDB clinical associates. The Physical Therapy Service performs manual muscle evaluations, objective measurements of strength, and pulmonary function studies prior to commencement of therapy, and repeats these evaluations from time to time. One evaluation requires three hours of a therapist's time. Thirty-six patients have been so evaluated for a total of 50 evaluations to March 1964. It is estimated that 10 additional patients will be evaluated by the end of June 1964.

Electromyography:

Demands on the Electromyography Service increased substantially for the period. Three procedures are routinely requested and performed, viz., electromyography, measurement of nerve conduction velocity, and repetitive nerve stimulation. In the period January 1, 1963, through June 30, 1964 (May and June of 1964 are estimates), we saw 318 patients for the electromyographic study of a total of 950 muscles; 161 patients for measurement of conduction velocity of 352 nerves; and 11 patients for stimulation studies. As expected, the majority of consultation requests were received from NINDB (297). All other Institutes sent a total of 30 consultation requests (15 from NIAMD, 6 from NCI, 5 from NHI, and 4 from NIAMD).

It is estimated that one EMG study averages 2 1/2 hours of time on the part of one of the Rehabilitation Department's medical officers; a nerve conduction velocity study averages 1 1/2 hours; and a stimulation study averages 3 hours. Included in these estimates is the time it takes to inspect the film record of the procedure and make the necessary measurements and calculations preparatory to the report.

Childrens Program:

The occupational therapy program for children has been increasing steadily in direct proportion to the increase in the number of children admitted to the Clinical Center, particularly on NCI. Because of such increase, the space in the clinic was not adequate, and the alteration described below (under "Space") was made. The occupational therapy program for children with leukemia has been more closely integrated with procedures and treatments on the Nursing Units. This has been accomplished through the participation of the occupational therapist in the weekly conferences on 2E and 13E at which time the adjustment needs and other problems of individual patients are discussed.

Staff Training:

Miss Vida Jo Niebuhr, Chief, Physical Therapy Service, attended a one-week senior level orientation conference at HEW on Public Health Service Programs and Program Management. Miss Carol Wendell, staff physical therapist, attended a 1-week course in Lower Extremity Prosthetics given at New York University. In February 1964, Miss Niebuhr and Miss Wendell participated in a 3-day Institute of Physical Therapists sponsored by the American Hospital Association and the American Physical Therapy Association. The meeting was held in Washington, D.C.

Throughout the period, the Department provided orientation and training programs for its new staff members, and also participated in in-service training courses, orientation lectures, and the Rehabilitation Department tours for a large variety of Clinical Center personnel, including Gray Service volunteers, Social Service staff, Nutrition Department personnel, Nursing Department staff, and others.

Participation of Personnel in Professional Activities off the Campus

Miss Mary Beach, Chief, Occupational Therapy Service, and Miss Vida Jo Niebuhr, Chief, Physical Therapy Service, have continued to serve on their respective panels of the Board of the U.S. Civil Service Examiners for the Public Health Service.

Mrs. Andrea Perkins, staff occupational therapist, in charge of the Childrens Clinic, has accepted the invitation of Mrs. Sargent Shriver to act as Director of Arts and Crafts at the Kennedy Camp for Mentally Retarded Children at Rockville, Maryland, from June 8 to July 3, 1964.

Publications:

1. "The Function and Scope of the Physical Therapy Service at the National Institutes of Health", by Vida Jo Niebuhr, Physical Therapy Service, in the Journal of the American Physical Therapy Association, vol. 43, No. 10, October 1963.
2. "Physical Therapy for the Heart Surgery Patient", by Vida Jo Niebuhr, in the Journal of the American Physical Therapy Association, vol. 43, No. 11, November 1963.
3. "The Relation of Induced Dysnomia to Phoneme Frequency", by Judith K. Purnell (Lansdell), Speech Therapy Service, et al., in Language and Speech, vol. 6, part 2, April-June 1963.
4. "The Carotid Amytal Test", by Judith P. Lansdell, in Maryland Journal of Speech and Hearing, June 1964.

Equipment:

No purchases of new major equipment were made during the period.

Space:

Request was submitted in June 1963 for removal of unused therapeutic pool and conversion of the space into separate areas for use as an office for the Chief, Physical Therapy Service, a pulmonary function room, a storage room, and a ladies' dressing room. To date we have not been advised of any action taken on this request.

In February 1964, four modules were taken from Occupational Therapy Service and reassigned to Clinical Pathology Department. Thus, the entire area in which supplies for occupational therapy projects were stored and prepared for patient use was lost. To make space for these essential functions of the Service, the woodworking program had to be discontinued and the space converted to storage and preparation, with a portion of such supplies now kept in an adjacent office and treatment room. Power tools needed for preparation were moved into the Arts and Crafts Clinic, and are used only by personnel; some equipment was stored in the Physical Therapy Service; the remainder was surplused.

Because of increasing numbers of children referred, the Childrens Clinic was enlarged in October 1963 by one module taken from the adjacent General Clinic.

Personnel Changes:

A number of personnel resignations were effective during this period and new appointments were made. As of June 30, 1964, personnel totaled 27, with 1 vacancy in the Occupational Therapy Service.

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

PHARMACY DEPARTMENT

CC-42
Serial No.

The Pharmacy Department is composed of the following services: Pharmacy, Central Sterile Supply, Pharmaceutical Development, Radiopharmaceutical, and the Office of the Chief. During this 18 month period, the Department's activities have increased in several areas. Also, new areas of responsibility have been added. The bulk of the workload units of issue increase in the Department were in the Central Sterile Supply Service. The Radiopharmaceutical Service provided a considerable increased service as shown in the attached statistical data. The most dramatic increase in service requests was experienced in the Pharmaceutical Development Service. The total number of units prepared actually decreased but this is meaningless due to the size of batch variations. Following the initiation of new regulations by the Food and Drug Administration the requests increased 74% over the previous calendar year and slightly higher in fiscal year 1964. Further, this increased demand for service in the investigational drug field resulted in a rapid increase in the number of complete drug assays and the completion of "drug data sheets" for filing with the FDA.

The Department was required to register as a manufacturer of drugs. Although this involves no expense, the Department is unable to meet all the requirements as set forth in regulations governing manufacturers, particularly in the area of assays and quality control.

The Pharmacy Bulletin has been published during this period and contains review articles of timely professional subjects in addition to the normal pharmacy information.

Pharmacy's role in nursing education and orientation was increased to five lectures, each of one hour duration, covering the metric system, procedures and drug information.

The Pharmacy Catalog was revised and published to reflect the latest changes in stock items and procedures. It is interesting to note that there is approximately a 15% change in drug listings.

Additional space was obtained during the year and allocated for the following uses:

Assay laboratory
Quality control and sample retention area
Walk-in refrigerator for reserve drug storage
Dressing and bandage packaging

Intravenous additive laboratory (construction not completed)
Prepackaging area (awaiting construction)
Aerosol laboratory (awaiting personnel reporting on duty)

A continuing problem for the Department is the loss of good qualified professional personnel due to the inability to pay competing salaries while demanding better-than-average professional performance.

The problem causing most concern in every day operation is a lack of communication between clinicians establishing project needs and the provider of these needs - the Pharmacy Department. In the majority of cases, the projects are established and patients admitted prior to any notification to the Department that new service will be required. There should be communications stating whether the demands will be financially supported by the Institute or by Clinical Center funds.

Pharmacy Service -- The Pharmacy Service did not experience an increase in the total workload; however, the items dispensed increased in overall cost due to new and more expensive drugs. One example of a costly drug is Prednisolone Injection used by the National Cancer Institute. Approximately $2,000 worth of this drug is used per week, necessitating the support of the National Cancer Institute. Several new antibiotics were introduced, each more specific in action; however, this resulted in an increase of drug expenditure.

A 3-month pilot study of a centralized I.V. additive program was completed in January. As a result, this will become a permanent service to the Clinical Center in fiscal year 1965.

There remains a definite need for research into the stability of drugs added to intravenous solutions. All past studies have been based upon clarity as an indication of compatibility or stability. This is unsatisfactory and a more thorough study involving many actual assays is necessary to assure the clinicians of full activity or potency.

Recently the prepacking of tablets and capsules for inpatient uses was changed to include the use of a one-time-use bottle and label. This should assist the Pharmacy in the area of bottle reclaiming and cleaning in addition to providing a more completely labeled container to the nursing units.

Central Sterile Supply Service -- The units of issue in the Central Sterile Supply increased only 3% during fiscal year 1964 over calendar year 1962. However, this entire total was concentrated in the surgery packaging area. The increase in the workload units in the surgery packaging area increased 8%, including normal surgery supply increases for Building 10-A and the entire responsibility for processing cardiac catheters.

One piece of new-type equipment was purchased and put into use in the National Cancer Institute surgery area. This is a Jobst Air Pressure Bandage Machine being used by Dr. Alfred Ketcham.

The labeling of sterile and clean items for issue was improved by the receipt of a more advanced label preparation machine.

A recording potentiometer for the electric hot air sterilizing oven was installed, thereby making possible an improved quality control system on hot air sterilized items.

Additional information available on the ethylene oxide gas sterilizing method resulted in an increase to a 2-hour exposure period to assure a greater margin of safety.

Sterile disposable trays are being evaluated in several areas within the Clinical Center. After extensive evaluation in actual patient use, several sterile disposable trays are being used.

A complete Tray and Set Catalog was published and distributed to the nursing units to provide for the physicians and nurses a picture and a complete list of tray contents. This should assist users in ordering and opening only the correct trays for each procedure.

The I.V. additive program of the Pharmacy Service will require a change in the source of the basic intravenous solutions. In addition, this will require the orientation of hundreds of professional individuals in a new system of use; however, the end result should be an improvement of the entire I.V. procedures.

Disposable examining gloves are being used within the Clinical Center after several years of evaluation. Presently the possibility of using disposable surgical gloves is being evaluated and will be accomplished if found to be completely acceptable and advantageous.

Position descriptions were rewritten for all personnel to reflect the many changes occurring in the field of sterile and clean supplies.

Pharmaceutical Development Service -- The Pharmaceutical Development Service is responsible for the development and formulation of suitable dosage forms of drugs for clinical investigational use.

Strict registration in the control and dispensing of clinical investigational drugs is reflected to some extent by the increase of investigational drugs registered from 358 in 1962 (fiscal year), to 722 in 1964 (fiscal year).

The establishment of a quality control procedure for all products developed and formulated into dosage forms in the Pharmaceutical Development Service, for Clinical Center use, has aided the Clinical Center and the Institutes in their compliance with New Drug Regulations.

> All drugs used in man are registered with and dispensed through the Clinical Center Pharmacy. Since the enforcement of stricter FDA regulations, a large increase in investigational drug registration has been noted, indicating that all were not properly registered previously. Since the investigator is ultimately responsible for the identity and purity of the drug administered, the Pharmaceutical Development Service assists the investigator by supplying formulation, assay and control procedures for the products and the necessary drug identity information which is forwarded to the Food and Drug Administration.

The drug identity information is a new standard means of providing the Clinical Research Committee and the Food and Drug Administration with information on investigational drugs in the Clinical Center, NIH. A description of the mechanism on how each is prepared is forwarded by the Clinical Center Pharmacy Department to the Food and Drug Administration for inclusion in their master file # MF 569.

In keeping with the new FDA regulations, the Pharmaceutical Development Service has expended much effort in the preparation of Analytical Data Sheets.

National Heart Institute	24
National Cancer Institute	14
National Institute of Arthritis & Metabolic Diseases	20
National Institute of Allergy & Infectious Diseases	2

Equipment of note received during the year to aid in the processing and assaying of material includes:

1. RePP #16 Lyophilization Apparatus
2. Gilson Volumetric Fractionator

PROBLEMS

One of the major problems confronting the Pharmaceutical Development Service is the staffing of the Service with highly qualified personnel. In the Research, Product Development, and Analytical & Quality Control Laboratory, qualified men with definite training and background in these areas are needed. During the year, the Pharmaceutical Development Service has lost two qualified men -- one with M.S. degree and one with B.S. degree with industrial experience -- to other branches of the Service. Their reasons for leaving included: the Clinical Center's inability to provide further outside-the-Service training and education, lack of rapid advancement, and low salaries.

The relationship of the Pharmaceutical Development Service and the Cancer Chemotherapy National Service Center continues to be of some concern in the Clinical Center Pharmacy.

Working relationships with the National Cancer Institute clinicians in the Clinical Center and the Pharmaceutical Development Service at times are strained due to the inability of the CCNSC to provide investigational drugs needed in research studies.

Frequently, the supply of a drug is exhausted mid-way in a study and more of the drug cannot be obtained at that time. Lag periods of a few days to a few months have been known to occur. The clinician is then disturbed with the Pharmacy Department because of the unavailability of the drug, when actually the CCNSC is responsible for the lack of the drug.

A most important subject of concern is the quality of the investigational drugs received from the CCNSC. In the past year a number of investigational drugs have been found to be low in potency upon actual assay in the Pharmaceutical

Development Service. Valuable time and research money are lost due to the use of drugs low in activity or low in potency. Proper quality control and storage stability studies are not being carried out by the CCNSC. The Pharmaceutical Development Service continually attempts to assay and check the quality of all products received from the CCNSC; however, the lack of proper assay personnel makes this feat impossible.

In order for the Pharmaceutical Development Service to make any kind of advancement in years to come, recruitment of the best possible men in the Public Health Service is needed. If they cannot be recruited from the Service, they should be obtained from other sources.

Radiopharmaceutical Service -- Additional space provided during the 18-month period covered by this report has considerably relieved the Service of some serious problems noted in the past. The assignment of a full-time clerk-typist has also greatly assisted us in fulfilling our mission and responsibility in this area.

Workload figures again show a large increase in services provided. The Radiopharmaceutical Service has continued to provide, for the use of authorized clinical investigators, properly formulated radioactive dosage forms, many of which are unavailable from any other source. An example of a new product provided during this period is Aggregated Human Serum Albumin labeled with Iodine-125. The albumin was aggregated by a process of heat denaturation under very closely controlled conditions of pH, time, and asepsis, and the resultant protein was then tagged with the radionuclide. After control testing, the product was utilized in studies of the reticuloendothelial system by investigators of NIAID.

In collaboration with investigators in the NINDB Section on Neuroradiology and the Clinical Center Diagnostic X-Ray and Radiation Safety Departments, this Service has contributed to early pilot studies in animals of a new, short half-life scanning agent, Technetium-99m. Use of this material in Clinical Center patients will begin very shortly, based upon the favorable results noted in these pilot studies. The route of administration of this compound may be oral, intravenous, or intrathecal, depending upon the formulation method used.

Continued close liaison with the Radiation Safety Department and the Radiation Committee has resulted in excellent control over the use of radioactive materials in Clinical Center patients.

Consultations continue to be a very important part of the Radiopharmaceutical Service function. These consultations develop from many intramural sources in addition to domestic and foreign sources. Examples are:

> Consulted by Dr. S. Kato, Executive Managing Director, Dainabot Radioisotope Lab., Ltd., Tokyo, Japan, concerning research and development problems.
>
> Consulted by Dr. Rene Masseyeff, Faculte de Medecine at Dakar-Senegal, Africa: Protein Labeling.

Consulted by Michael Schwartz, M.D., Copenhagen, Denmark, concerning Human Serum Albumin-Cr^{51}.

Consulted by T. Manovtcherian, M.D., Medical School Faculty, University of Tehran, Iran, concerning radiopharmaceutical formulation.

Consulted by Dr. Albert Q. Butler, a member of the General Committee of Revision of the United States Pharmacopoeial Convention, concerning radiopharmaceutical monographs for USP XVII.

Major Problems

Two major problems exist. One of these is a continuing one, and relates to the limit of one pyrogen test of a radiopharmaceutical product per day. This limitation results in delays for clinicians, problems in the scheduling of formulation procedures, and perhaps worst of all, the tendency of clinical investigators to use the Statement of Responsibility and Certification of Drug Release Form in order to utilize a product awaiting test in situations which ordinarily would not require the use of this mechanism.

The second one is concerned with the scheduling of procedures in which extremely short half-life radionuclides are used. Frequently, this required the services of a radiopharmacist on extremely short notice and for long periods of time, thus delaying other procedures that were scheduled in the laboratory. Examples of these types of compounds are Iodine-132 and Technetium-99m.

PHARMACY DEPARTMENT STATISTICAL DATA

	1961 (Fiscal)	1961 (Calendar)	1962 (Fiscal)	1962 (Calendar)	1963 (Calendar)	1964* (Fiscal)
Total number of units issued	3,983,327	4,097,653	4,204,384	4,427,821	4,348,298	4,528,914
Pharmacy Service						
Prescriptions	26,570	29,383	31,867	32,480	30,685	31,700
Other items	251,598	262,414	268,057	295,806	289,844	301,994
Prepackaged items	64,132	71,093	73,121	67,857	59,013	53,199
Total	342,300	362,890	373,045	396,143	379,542	386,893
Central Sterile Supply Service						
Units issued	3,602,498	3,691,857	3,785,547	3,980,942	3,923,710	4,100,580
Pharmaceutical Development Service						
Units developed and issued	36,819	41,427	44,113	48,552	41,796	37,536
Requests processed	1,423	1,935	1,911	2,033	1,959	2,148
Investigational drugs registered	298	321	358	402	702	722
Radiopharmaceutical Service						
Units developed and issued	1,710	1,479	1,679	2,184	3,250	3,905
Requests processed	311	330	453	571	938	1,130
Pharmacy Officer of the Day						
Number of requests for service	1,240	1,134	1,268	1,463	1,658	1,867

*Totals are estimated for May and June 1964

Publications

Skolaut, M.W.: The formulary system. Amer. Prof. Pharm.: 36-37, June 1963.

Skolaut, M.W.: Here are 5 sound suggestions for drug procurement. Amer. Prof. Pharm.: 34-37, Aug. 1963.

Skolaut, M.W.: Opportunities for leadership. Amer. J. Hosp. Pharm. 20: 391-392, Aug. 1963.

Skolaut, M.W.: Report of committee on resolutions. Amer. J. Hosp. Pharm. 20: 404, Aug. 1963.

Skolaut, M.W.: Application of quality control procedures in the hospital pharmacy. Hospitals: May 1964.

Skolaut, M.W.: Glass hypodermic syringes and methods of sterilization. Amer. J. Hosp. Pharm.: April 1964.

Briner, W.H.: The preparation of radioactive chemicals for clinical use. Amer. J. Hosp. Pharm. 20: 553-561, Nov. 1963.

Briner, W.H.: Radiopharmaceuticals. In Sprowls, J.B., Jr. (Ed.): Prescription Pharmacy. Philadelphia, J.B. Lippincott Co., 1963, pp. 525-559.

Briner, W.H.: Report of committee on radiopharmaceuticals. Amer. J. Hosp. Pharm. 20: 408, Nov. 1963.

Briner, W.H., Gordon, R.S., Jr., and Waldmann, T.: Principles in the production and formulation of I^{131} labeled polyvinylpyrrolidone and CR^{51} labeled serum albumin for parenteral use. In Schwartz, P. and Vesin, P. (Eds.): Plasma Proteins and Gastrointestinal Tract In Health and Disease, Proceedings of the International Symposium in Paris, Aug. 1961. Copenhagen, Munksgaard, 1963, pp. 85-89.

Gallelli, J.F. and Kostenbauder, H.B.: Kinetics of base-catalyzed hydrolysis of trimethadione. J. Pharm. Sci. 52: 649-656, July 1963.

Pierpaoli, P.J.: Some administrative considerations in assigning responsibility for central sterile supply service. Amer. J. Hosp. Pharm. 20: 370-371, Aug. 1963.

Professional Activities

Milton W. Skolaut

President of the American Society of Hospital Pharmacists.

Member of instructional staff of five institutes on General Practice of Pharmacy.

Many lectures and speeches to Hospital Pharmacy groups across

the United States representing the American Society of Hospital Pharmacists.

William H. Briner

Elected President, Mid-Eastern Chapter of the Society of Nuclear Medicine; member of the Executive and Nominating Committees, Society of Nuclear Medicine.

Member, Advisory Panel of The National Formulary.

Chairman, Committee on Radiopharmaceuticals of the American Society of Hospital Pharmacists.

Member, Joint Committee of the American Association of Colleges of Pharmacy and the American Society of Hospital Pharmacists.

Speeches

William H. Briner

Lectured at the NIH Radioisotope Courses offered by the Radiation Safety Department.

Participated in Symposium on Tracer Methodology in Chicago, Illinois.

Faculty member in ASHP-DRH Basic Radiological Health Course.

Lectured at 1964 Pharmacy Assembly conducted by the New York State Council of Hospital Pharmacists in West Point, New York, May 1964. "Handling Radiopharmaceuticals by the Hospital Pharmacist".

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

MEDICAL RECORD DEPARTMENT

CC-46
Serial No.

OBJECTIVES

The Medical Record Department has the major responsibility of insuring the completeness, accuracy, safekeeping, and availability of medical records and maintains the following internal controls: (1) Continual appraisal of the medical records of patients registered at the Clinical Center, in order to maintain the standards established by the Clinical Center and accrediting agencies. (2) Maintenance of required indexes; namely, the analysis of discharged patients and the diseases and operations index with a view toward providing adequate basic data to physicians participating in medical research. (3) Maintenance, compilation, and distribution of statistical data concerning patient care for utilization by administrative, clinical, and research directors. (4) Maintenance of a systematic arrangement of medical records to insure their immediate accessibility for purposes of patient care service and medical research. (5) Maintenance of a system whereby the quantity and quality of dictated medical record reports are controlled. (6) Maintenance of an adequate control system with regard to the release of medical reports, medical information, and medical records to authorized recipients. (7) Maintenance of a perpetual patient's index (Soundex) and patient registry.

MAJOR PROGRESS

Education and Training. Orientation of new employees of this Department, other Clinical Center Departments, and the Institutes was accomplished. Lecture tours continue to be given to PHS medical record librarian students and other visitors to the Clinical Center.

Key personnel attended seminars, institutes and an international congress on subjects relating to medical record organization and management, automatic data processing, and new office equipment. Lectures on a variety of clinical subjects were attended also.

A 19-hour course in Basic Medical Terminology, supplemented with a lecture series given by physicians, was conducted to increase the capability and versatility of personnel.

In August 1963 the Transcribing Unit was transferred to Building 31, thereby decentralizing the Department. The move has proved to be a satisfactory arrangement and the usual services continue to be rendered efficiently.

Personnel. The number of employees on duty 31 March 1964 was 80; of this number 18 served on a part-time basis.

Departmental Activities. The Personnel audit of jobs was completed.

A total of 107 physicians were cleared of medical record responsibilities.

The offset duplicating equipment and responsibility for duplicating medical and selected administrative reports were transferred to the Office Services Branch, Office of the Director, NIH.

The Medical Record Files and Research Units were consolidated into the Control and Processing Section in order to provide for work simplification and efficient and uniform flow of work.

Due to the lack of adequate filing space, it was necessary to discontinue maintaining extra copies of reproduced medical reports and to seek additional filing space for retired medical records.

The NCI Record Office was discontinued in September 1963. All special procedures relating to the processing of NCI incomplete records were also discontinued. These records are now processed in accordance with the procedures in force for all other Institutes.

Due to a large backlog of incomplete charts, measures were instituted for corrective action. Currently, any physician who has patient records that have been incomplete for more than two months will not have records sent to him, routinely, for completion. Instead, all records are held for him to complete in the Medical Record Department. Clinical Directors are notified each month regarding the number and type of deficiency for each physician in their Institute.

PRODUCTION

The production report is based on work performed during Calendar Year 1963 and the first quarter of Calendar Year 1964, consisting of 316 actual working days and 2312½ hours of overtime which were approved and reported.

The Research and Statistics Section reviewed and circulated incomplete medical records daily; there were 792 incomplete records for the period from 10 April 1962 through 15 March 1964. There were 124 medical and statistical studies completed. The coding and indexing for the period from July 1953 through December 1960 has been completed, with the exception of nine medical records which have been reported as lost. The number of cases coded and indexed was 2399. The status of the coding and indexing for discharges in the remaining calendar years is summarized as follows:

	Calendar Years			
	1961	1962	1963	Jan. - Mar. 1964
Number of Discharges	3863	4134	3882	949
Completed as of 31 March 1964	3742	1933	33	0
Remaining as of 1 April 1964	121	2201	3849	949

The Files Section processed and delivered a total of 146,328 medical records for purposes of review and study, 2,931 medical records relating to inpatient readmissions and 24,699 medical records relating to follow-up visits. A total of 37,751 masters was reproduced by offset duplication. Material reproduced by verifax numbered 28,222; the material included clinical reports, correspondence, insurance forms and other related material.

The Transcribing Section's work production is summarized as follows:

	Calendar Year 1962	Calendar Year 1963	% of Decrease
Discs Received	9,292	8,614	.073
Discs Transcribed	9,199	8,740	.049
Material Transcribed (Pages)	29,524	27,977	.052
Remaining Work	287	52	.81

The Medicolegal Section received, screened, completed or prepared for mailing 13,719 pieces of material.

MAJOR PROBLEMS

Coding and Indexing. Lack of sufficiently trained personnel has restricted the progress of the coding and indexing of diagnoses and operations.

Location of Medical Records. In spite of extensive controls, physicians repeatedly fail to take precautions relating to the safeguarding of medical records which have been placed temporarily in their custody.

Lost Medical Records. Exhaustive searches are made when it is apparent that a record is temporarily misplaced. During this reportable period two records have been declared permanently lost; there is a total of 14 reported lost medical records since the Clinical Center opened in July 1953.

PROPOSED FUTURE OBJECTIVES

Eliminate the backlog in coding and indexing of diagnoses and operations.

Reduce the number of incomplete medical records. Our goal is to assure that the number of incomplete records does not exceed the total number of discharges for any given month.

Convert the coding system from the Standard Nomenclature of Diseases and Operations to the International Classification of Diseases, Adapted.

STATISTICS - Period Covered: 1 January 1963 through 31 March 1964

I. Registration

A. Patients		8,276
Inpatients	4,865	
First registration	1,934	
Readmission	2,931	
Follow-up patients (first registration)	3,364	
Walk-in	20	
Emergency	27	
B. Employee registration		2,984

II. Patient Care Statistics

Total number of admissions	4,865
Percentage of Decrease, CY 1963 admissions compared to CY 1962	7%
Total number of discharges (includes 261 deaths)	4,831
Total patient days	170,476
Available bed days	235,296
Average daily census	374
Average length of stay	38
Percentage of occupancy	72
Total number of deaths	261
Percentage of deaths	5%
Total number of autopsies	245
Percentage of autopsies	94%
Discharged patient days	185,158
Total number of patients admitted from 6 July 1953 through 31 March 1964	32,354
Percentage of patients admitted during CY 1963 and the first quarter, 1964 from Maryland, Virginia and the District of Columbia	43%
Number of admissions - 16 and under	1,008
Number of admissions - 14 and under	897

PEDIATRIC STATISTICS - 16 and under

Total pediatric discharged patient days - CY 63 + 1st Qtr. 64.	28,214
Total pediatric discharges	987
Average length of stay, pediatric	29
Total pediatric inpatient days	30,670
Total actual bed days - all Institutes	170,476
Percentage of actual bed days utilized by pediatric	18%

ANNUAL REPORT, STATISTICS--PERIOD COVERED: 1 January 1963 - 31 March 1964

I. Grand Total: Discharged Inpatients

Calendar Year	1956	1957	1958	1959	1960	1961	1962	1963	Jan-Mar. 1964
	2,369	2,865	3,275	3,485	3,658	3,863	4,134	3,882	949

II. Total, Discharged Inpatients by Geographic Area:

Geographic Area	Patients Discharged								
	Calendar Year								Jan-Mar.
	1956	1957	1958	1959	1960	1961	1962	1963	1964
D.C.	551	610	602	560	522	412	473	386	93
Maryland	589	799	810	760	797	748	780	717	171
Virginia	377	478	442	598	564	596	597	558	158
TOTALS	1,517	1,887	1,854	1,918	1,883	1,756	1,850	1,661	442

Geographic Area	Percentage								
	Calendar Year								Jan-Mar.
	1956	1957	1958	1959	1960	1961	1962	1963	1964
D.C.	23	21	18	16	14	11	11	10	10
Maryland	25	28	25	22	22	19	19	18	18
Virginia	16	17	13	17	15	15	14	14	17
TOTALS	64	66	57	55	51	45	45	43	44

Attachment

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

NURSING DEPARTMENT

CC-51
Serial No.

PROGRAM GOALS

Major goals of the Nursing Department during the past 18 months were: (a) To provide, with the staff available, the best possible nursing care to patients; (b) to provide competent assistance to the clinical investigators; (c) to orient, train, and supervise personnel so that they may become increasingly proficient in carrying out (a) and (b); and (d) to constantly evaluate and improve nursing practice and nursing administration.

PROGRESS MADE

A review of the projected plans for 1963 reveals that other than continuing in our efforts to meet our major program goals, we have been unable to carry out our plans for additional activities because of the increasing workload and a decreased nursing staff.

DEVELOPMENTS AND TRENDS

The last year and a half was a busy period. The number of very ill patients remained consistently high, and the nursing staff has been reduced. Recruitment of staff still remains a serious problem. There have been a number of changes in the research programs which have increased the workload substantially. For example:

(a) Clinical investigators of the National Cancer Institute and the National Heart Institute have requested that nursing coverage in the Admissions and Followup Department be provided on weekends and holidays, as they wish to schedule appointments for certain patients at these times. Beginning February 10, 1964, one nurse has been assigned to work 8 a.m. to 4:30 p.m. on Saturdays, Sundays, and holidays.

(b) The number of in-patients examined and treated in the Admissions and Followup Department is increasing. During fiscal year 1963, there were 2,445 in-patient visits in contrast to 1,684 in fiscal year 1962.

(c) On the Arthritis and Metabolic Diseases Nursing Service, there is an increasing number of adult patients with systemic lupus erythematosus and Sjörgren's syndrome, and children with juvenile rheumatoid arthritis. It is likely that the number of metabolic balance studies will be increased to at least 12 simultaneously.

(d) The workload on the Cancer Nursing Service has been constantly increasing:

(1) The number of very ill and moribund patients continues to be high.

(2) The number of patients on intravenous therapy on 2 East and 13 East has markedly increased. The number of bottles of admixtures and of units of blood and blood products administered on these two units during fiscal year 1963 increased by 15,787 over the number given the previous fiscal year.

(3) More major surgical procedures were performed due to an increase in the number of projects and in the number of senior surgical staff members.

(4) Subarachnoid perfusions, which are complex and time consuming, are being done on some patients with leukemia, particularly if there are symptoms which indicate meningeal irritation.

(5) The number of children and young adolescents being admitted for treatment and study is increasing.

(6) The number of patients having plasmapheresis is increasing to the point where a special laboratory and staff are necessary to handle this procedure on Dr. Frei's service.

(e) Opening of the new surgical wing in mid-1963 has greatly increased the workload for the Surgical Nursing Service and for the Heart and Neurology Nursing Services. As many as nine major cardiac surgical procedures have been performed within one week. The average is four to six such procedures each week. In addition, ten or more cardiac catheterizations

are done each week.

(f) All units on the Heart Nursing Service were moved during the past few months. This was a sizeable project and was accomplished smoothly and efficiently.

(g) Staffing on the Psychiatric Nursing Service has been minimal and sometimes at a dangerously low level much of the past year. Considerable changing of time and scheduling of staff to work overtime have been necessary. Even so, it has not been necessary to make major changes in the clinical research projects.

(h) Next fiscal year, a four-bed post-operative recovery unit will be opened on the tenth floor adjacent to the operating rooms. This space will accommodate post-surgical patients from services other than Cancer who have been "boarders" on 10 East and receiving 24 to 72 hours of post-operative care.

MAJOR PROBLEMS

The major problems remain the same:

(a) Shortage of personnel and increasing demands for services.

(b) Non-segregation of children, except on the Cancer Nursing Service.

(c) Lack of central storage space for children's furniture, as well as for other large items of furniture and equipment.

(d) Lack of play and recreation space on the units for children.

(e) Absenteeism and unscheduled absences of staff members.

ACCOMPLISHMENTS

1. Publications

(a) Fitzwater, Janet: Bacteriological Studies of Open and Closed Cabinets in the Operating Room. Hospital Topics, 1963.

(b) Fitzwater, Janet: Scrub Sinks Harbor Potential Danger. AORN Jour. 1: 36-37, 1963.

(c) Fitzwater, Janet: Suture Holder. The Amer. J. Nurs. 63: 91, 1963.

(d) Fitzwater, Janet: Issues Regarding Standards for Nursing Care in the Operating Room - Viewpoint of the Supervisor. Professional Responsibility for Nursing Care of the Surgical Patient (pamphlet). Amer. Nurses' Association, New York, N. Y., 1963: 27-30.

(e) Fitzwater, Janet: Thoractic Screen. Amer. J. Nurs. 63: 100, 1963.

2. Video Tape Recordings for Teaching Purposes

Colostomy Irrigation

Oral and Pharyngeal Impairment in the Infant

Measuring Blood Pressure

Introduction to Research

Part I. Medical Research

Part II. Nursing Research

Salt and Water Balance

3. Other

(a) Chief, Psychiatric Nursing Service, served on the Board of Directors of the Washington Area Council on Alcoholism.

(b) Chief, Nursing Department, served on the Special Committee on Nursing Service of the American Nurses' Association.

(c) Dr. Jane Wilcox, Special Assistant for Nursing Research, served on the Executive Board of the Council on Medical Television.

PHS - NIH
Individual Project Report
Calendar Year 1963

Part A

Project Title:

A Study of the Use of Closed Circuit Television as a Tool for Making Observations in Studies of Nursing Care.

Principal Investigator:

Dr. Jane Wilcox

Cooperating Units:

Television Engineering Unit, CC

Man Years (computed for 12-month period)

Total: .80 man years

Professional: .55 man years

Other: .25 man years

Project Description:

a. Objective:

To explore the use of direct observation by means of a closed circuit television system as a means of studying nursing care while it is being given.

b. Methods Employed

(1) A single-patient room was made available by the National Cancer Institute for trial of the television system.

(2) Various types of closed-circuit television equipment were tried and evaluated with the advice and assistance of the CC Television Engineering Unit.

c. Major Findings:

(1) The use of a closed circuit television system provides a very effective observational tool for nursing research projects.

(2) Both patients and staff accept the closed-circuit television observations well when they are carefully prepared for the experience, when they always know when they are observed, and when they can freely choose to participate or not.

(3) The most effective types of equipment and facilities for such a system have been defined.

d. Significance:

The development of this method of observation is of great importance for nursing research because of a felt need for more studies of clinical nursing practice in its natural setting.

e. Proposed Course of Project:

This project is completed to the extent to which the situation at the Clinical Center permits. Evaluation of the use of video tape recordings was inadequate. Lack of funds for equipment did not permit doing more with this. A paper about this project is to be published in the journal, Nursing Research.

Part B

Not included.

PHS - NIH
Individual Project Report
Calendar Year 1963

Part A

Project Title:

The Life Situation of the Metabolic Research Patient

Principal Investigator:

Dr. Jane Wilcox

Cooperating Units:

National Cancer Institute
Cancer Nursing Service, CC

Man Years (computed for 12-month period)

Total: .70 man years

Professional: .45 man years

Other: .25 man years

Project Description:

a. Objectives

(1) To observe the natural history of events in the life of a metabolic research patient at the Clinical Center.

(2) To classify and analyze the behavior of a metabolic research patient as it occurs in his room at the Clinical Center.

(3) To describe the part played by nursing personnel in the life situation of the metabolic research patient.

(4) To develop hypotheses for experimental studies of nursing action in the care of metabolic research patients.

b. Methods Employed

(1) A small number of patients participating in metabolic balance studies have been observed in a patient room by two nurse observers by means of a closed-circuit television system.

(2) Data was collected by a system of written notations made during live television observations. Three hours of video tape recordings were made. Video tape recording could not be continued because of problems with facilities and equipment.

(3) Conferences and group discussions with nursing staff provided an understanding of the staff's perception of the life situation of the patient and the part played by nursing staff in this situation.

c. Major Findings

The number of patients observed is not sufficient to permit generalization. Analyses done or in progress have helped to develop ways of categorizing and interpreting the data which would be useful when more data might be collected.

d. Proposed Course of Project

Two things should be done to carry this project ahead: Observations should be made on a unit where more patient material is available, and facilities for video tape recording of observations should be provided.

Part B.

Not included.

Serial No. CC-51

PHS - NIH
Individual Project Report
Calendar Year 1963

Part A

Project Title:

An Exploration of the Use of Closed-Circuit Television in In-service Education in Nursing.

Principal Investigator:

Dr. Jane Wilcox

Cooperating Unit:

Television Engineering Unit, CC

Man Years (calendar year 1963):

Total: .80 man years

Professional: .55 man years

Other: .25 man years

Project Description:

a. Objectives

(1) To explore various methods of using closed-circuit television in the in-service education activities and in the orientation and training programs of the Clinical Center Nursing Department.

(2) To stimulate the interest of the staff of the Clinical Center Nursing Department in experimenting with the use of television for teaching.

b. Methods Employed

(1) As opportunities to do so have arisen, the nursing research staff has offered assistance and advice to others in the Department for the use of television in on-going in-service education activities.

(2) Television has been used for preparation of filmed instructional materials for units of teaching for which the staff of the Research Program are responsible.

c. Major Findings

(1) The effectiveness of television as a teaching medium has been demonstrated in various kinds of in-service education activities.

(2) There seems to be little interest in or acceptance of the use of instructional television at the senior administrative level.

d. Proposed Course of Project

Further experimentation with the effectiveness of television for in-service education in nursing would not seem to be necessary, the effectiveness having been shown. However, a study of why the use of television is not better accepted by the senior administrative staff might be of interest.

Part B Honors, Awards, and Publications

There were no publications related to this project in 1963. Six video tapes were produced:

(1) Colostomy Irrigation

(2) Oral and Pharyngeal Impairments in the Infant

(3) Measuring Blood Pressure

(4) Introduction to Research

Part I - Medical Research
Part II - Nursing Research

(5) Salt and Water Balance

NURSING DEPARTMENT
NUMBER OF HOURS OF OVERTIME BY SERVICE
July 1, 1962 - December 31, 1963

Nursing Service	Fiscal year 1963 7/1/62 - 6/30/63	Calendar year 1963 1/1/63 - 12/31/63
	Hrs.	Hrs.
Admissions and Followup----------	306.00	281.50
Allergy and Infectious Diseases---	222.00	329.50
Arthritis and Metabolic Diseases--	263.75	221.50
Cancer----------	1,842.00	2,061.75
Heart----------	197.25	162.75
Neurology----------	400.50	281.50
Psychiatry----------	904.50	1,161.50
Surgery----------	1,269.25	1,513.50
Total----------	5,405.25	6,013.00
Number man days----------	675.70	751.60
Number man years----------	2.90	3.30

NURSING DEPARTMENT
HOURS OF CONTINUOUS NURSING CARE
PROVIDED BY EACH NURSING SERVICE
July 1, 1962 - December 31, 1963

Nursing Service	Fiscal year 1963 7/1/62 - 6/30/63	Calendar year 1963 1/1/63 - 12/31/63
	Hrs.	Hrs.
Allergy and Infectious Diseases----	3,349.00	6,927.5
Arthritis and Metabolic Diseases---	3,749.00	3,367.5
Cancer----------	15,177.25	17,352.0
Heart----------	20,911.75	19,491.5
Neurology----------	8,622.50	5,871.5
Psychiatry----------	3,329.75	3,576.0
Total----------	55,139.25	56,586.0
Number of man days----------	6,892.40	7,073.45
Number of man years----------	29.96	30.75

NUMBER OF HOURS OF NURSING CARE GIVEN
BY PART-TIME PROFESSIONAL NURSES (WAE)
ON EACH NURSING SERVICE
July 1, 1962 - December 31, 1963

Nursing Service	Fiscal year 1963 7/1/62 - 6/30/63	Calendar year 1963 1/1/63 - 12/31/63
	Hrs.	Hrs.
Admissions and Followup----------	1,418.00	735.00
Allergy and Infectious Diseases----	683.00	838.00
Arthritis and Metabolic Diseases---	3,040.50	2,910.50
Cancer----------	16,092.00	18,386.25
Heart----------	5,474.00	5,961.50
Neurology----------	3,283.00	3,730.00
Psychiatry----------	2,862.00	4,354.00
Education and Training (orientation)----------	424.00	1,059.00
Total----------	33,276.50	37,974.25
Number man days----------	4,159.56	4,746.80
Number man years----------	18.08	20.60

NURSING DEPARTMENT
DAILY AVERAGE PEDIATRIC CENSUS
BY AGE GROUPS

Age group	Fiscal year 1963 7/1/62 - 6/30/63	Calendar year 1963 1/1/63 - 12/31/63
Under 16 years of age-------	70.20	67.20
Under 14 years of age-------	57.10	57.40
Under 6 years of age--------	27.40	28.04
Under 2 years of age--------	8.34	7.08
2 - 5 years of age----------	19.05	20.83
6 - 13 years of age---------	29.60	29.31
14 - 16 years of age--------	13.14	9.90

NURSING DEPARTMENT
DAILY AVERAGE PEDIATRIC CENSUS
ON EACH NURSING SERVICE

Nursing Service	Fiscal year 1963 7/1/62 - 6/30/63	Calendar year 1963 1/1/63 - 12/31/63
Allergy and Infectious Diseases-------------------	6.87	4.10
Arthritis and Metabolic Diseases-----------------	9.26	9.20
Cancer Nursing Service-----	24.50	26.70
Heart Nursing Service------	11.90	11.70
Neurology Nursing Service--	14.94	14.37
Psychiatric Nursing Service	1.60	1.06

NURSING DEPARTMENT
ACCESSIONS AND SEPARATIONS BY GRADE
July 1, 1962 - December 31, 1963

Grade	Accessions	Separations
	No.	No.
Supervisor GS-11 and above	2	3
Head Nurse, GS-9	5	7
Staff Nurse, GS-7	19	50
Staff Nurse, GS-5 and -6	174	136
Secretary, GS-4 and -5	2	5
Unit Clerk, GS-3 and -4	31	31
Practical Nurse, GS-3 and -4	29	27
Nursing Assistant, GS-2 and -3	67	85
Total	329	344

NURSING DEPARTMENT
NUMBER OF PERSONNEL AND YEAR OF EMPLOYMENT
BY GRADE AND POSITION AS OF
February 1, 1964

Year of employment	Senior Staff GS-11 and above	Head Nurse and Supervisor GS-9	Staff Nurse GS-7	Staff Nurse GS-5 and GS-6	Practical Nurse GS-3 and GS-4	Nursing Assistant GS-2, GS-3, and GS-4	Clerical staff all grades	Total
	No.	No.	No.	No.	No.	No.	No.	No.
1952	2	-	-	-	-	-	-	2
1953	8	6	9	-	4	12	2	41
1954	1	5	7	-	4	3	2	22
1955	2	8	11	1	12	9	0	43
1956	5	2	7	2	8	2	2	28
1957	2	6	7	0	10	11	2	38
1958	0	3	11	0	9	9	0	32
1959	0	2	10	2	9	4	1	28
1960	0	1	13	1	11	1	4	31
1961	1	3	11	4	13	12	3	47
1962	2	3	11	20	6	27	12	81
1963	0	1	17	72	18	26	18	152
1964	0	0	0	9	4	7	1	21
Total	23	40	114	111	108	123	47	566

HOURS OF LEAVE TAKEN
NURSING DEPARTMENT
FISCAL YEAR 1963

Type of leave	Professional staff	Nonprofessional staff	Clerical staff	Total staff
Daily average number of personnel	284.30	244.80	43.40	572.50
Annual Leave				
Total hours taken	33,083.00	28,871.00	4,845.00	66,799.00
Average hours per person	116.36	117.90	111.60	116.60
Average work days per person	14.50	14.70	13.90	14.60
Sick Leave				
Total hours taken	20,009.00	19,433.50	3,670.00	43,112.50
Average hours per person	70.30	79.40	84.50	75.30
Average work days per person	8.80	9.90	10.60	9.40
Other Leave				
Total hours taken	11,235.00	7,880.50	2,792.75	21,908.25
Average hours per person	39.50	32.20	64.40	38.30
Average work days per person	4.90	4.05	8.05	4.80
Total Hours, all Leave	64,327.00	56,185.00	11,307.75	131,819.75
Average hours per person	226.20	229.50	260.50	230.25
Average work days per person	28.30	28.70	32.60	28.75

January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

NUTRITION DEPARTMENT

CC-61
Serial No.

I. CONTRIBUTIONS TO THE CLINICAL RESEARCH PROGRAM

The role of the Nutrition Department of the Clinical Center, an all-research hospital, is necessarily unique. At the Clinical Center, the Nutrition Department not only assumes the usual responsibilities of hospital food service, but also takes an active part in the clinical research program. Because of the exacting requirements of its responsibility to provide investigators with services to assist and support them in their research programs, the Nutrition Department can delegate no part of the patient food service to other departments, as is done in other hospitals, but must accept full responsibility for the entire operation.

The Nutrition Department's contribution to the clinical research program can be measured not in terms of statistics, but in its development of valuable tools and techniques by means of which it can provide research investigators with precise and complete data on patient nutrient intake and thereby assist them in such activities as:

1. Interpreting the mode of action of new drugs.

2. Seeking additional knowledge of diseases for the purpose of developing new means of treatment.

3. Evaluating the course of a disease or the status of a patient.

4. Diagnosis.

One cannot review the monthly evaluation of the various patient units without being impressed with: the wide variety of dietary demands on each unit (most of which can be attributed to one of the four purposes given above); the variety in the type of patients serviced on each floor with respect to age, degree of illness, and on occasion, nationality; the contribution of dietary control to research; the recent upsurge of interest in fluid intake.

The March 27, 1964, research development report to the Surgeon General includes two new developments in which the Nutrition Department has given essential assistance.

The first development has been reported by NIAMD and NIMH scientists. They attribute homocystinuria, a newly discovered metabolic disease associated with mental retardation, to an enzyme defect.

Two Nutrition Department staff groups, those of the floor kitchen as well as the metabolic kitchen on the 9th floor, worked simultaneously to provide services and close diet control for the work of this study. The metabolic kitchen provided a diet of constant composition for an 8-year-old female patient with homocystinuria, for 65 days. To meet the needs of the study, the diet had to be constant and low in the amino acids methionine and cysteine, which, in turn, necessitated that it also be low in protein. Mullsoy formula, low in these amino acids, but having a taste not easily tolerated, was used as a source of protein. Otherwise, the diet consisted largely of vegetables, fruits, and cereal products. Great tact and patience were needed to get the patient, a feeble-minded child, to eat the total diet every day. Each meal period was supervised and, to assure the success of the study, the child was served at a table in the metabolic kitchen where a non-professional staff member told her stories or read to her to develop the essential rapport. As part of the study, the patient's parents were fed similar diets for 18 days, and an aunt was so fed for 10 days.

The 9th floor kitchen provided two of the patient's cousins (3 and 5 years old) constant low methionine, and low cysteine diets for 8 days.

The report is quoted, in part:

"Homocystinuria was first described in 1962. Elevated levels of homocysteine (a product of the metabolism of methionine) detected in the plasma of a patient with this rare disease suggested an 'overflow' of this amino acid into the urine. At the same time, increased levels of methionine in the plasma were noted. These observations suggested that the enzyme, cystathionine synthetase (which converts homocysteine to cystathionine, the precursor of cysteine), might be involved in the pathogenesis of the disorder. Although early studies by other investigators failed to confirm this hypothesis, the current investigators decided to test this theory directly.

"***These results suggest that, depending on his diet, an afflicted child may suffer from cysteine deficiency, particularly just after birth when the body's need for this amino acid is high and is probably met to a significant extent by conversion of the dietary methionine to cysteine. This deficiency of cysteine may be accentuated if the infant receives cow's milk because in contrast to human milk, it is relatively poor in cysteine. It is suggested that early supplementation of the diet with cysteine may prevent irreversible damage. Furthermore, cystathionine, the precursor of cysteine, is reportedly present in high concentration in the normal human brain, where it may serve some necessary function in addition to giving rise to cysteine. If this is so, dietary cystathionine supplementation might also be helpful. Whether abnormal accumulation of methionine and/or its metabolites contributes to the pathology in homocystinuria, and whether its dietary restriction is

warranted in this disorder, remains to be determined."

The second development reported deals with NHI studies which "indicate that plasma concentrations of high density lipoproteins may be determined by a single pair of allelic genes." The report states, "Tangier disease is a rare genetic disorder of lipid metabolism characterized by complete or nearly complete absence of plasma high-density lipoproteins (HDL), low serum cholesterol levels, and the accumulation of large quantities of cholesterol esters in reticuloendothelial tissues.

"These studies, together with studies on other syndromes characterized by plasma lipoprotein abnormalities, are helping to clarify the roles played by the various lipoprotein classes in lipid transport. Such knowledge has potential clinical importance because the distribution of plasma lipids among the various lipoproteins appears to be an important determinant of heart-disease risk."

Diet played a less prominent role in these studies. For the most part, the 6 patients studied were on regular diets. However, at selected periods, to assist with tests, diets of $1\frac{1}{2}$ to 2 grams of fat per kilogram of body weight were ordered for the patients' breakfasts. Predominantly saturated fats were used.

II. MAJOR PROBLEMS ENCOUNTERED

The fluctuating and unpredictable workload, influenced by nutritional aspects of research studies, continues as a problem because of budgetary and staffing restrictions. Examples of this are seen in the number of categories III and IV diet meals provided patients of each of the following Institutes in consecutive months of calendar year 1963:

	4,347 (June)			1,731 (Sept.)
NCI	3,180 (July)		NHI	2,913 (Oct.)
	-1,167			+1,182

Increased patient ration cost. Factors influencing the continued rise in cost are: (1) annual increases in wage and salary schedule of prevailing rate system jobs which make up approximately 80% of Nutrition Department staffing; (2) rising raw food costs; and (3) limited utilization of metabolic kitchens (the 12th metabolic kitchen has been closed for this reason).

Patient Ration Costs

Fiscal Year:	1961	1962	1963	1964 (thru' Feb.)
Personnel :	$ 8.11 (81%)	$ 8.23 (80%)	$ 8.63 (80%)	$ 9.70 (82%)
Raw Food :	1.63	1.65	1.70	1.79
Sup.& Other:	.29	.46*	.44	.39
Average cost per ration:	$10.03	$10.34	$10.77	$11.88

*(17¢ increase due largely to purchase of special supplies for NIAID virus study).

The low patient census of metabolic kitchens continues as a problem, although it was alleviated to some extent by discontinuing the 12th metabolic kitchen, effective October 31, 1963. In fiscal year 1963, balance study patients for the 3-B kitchen (NCI) averaged $2\frac{1}{2}$ to 3; 9th (NIAMD), $4\frac{1}{2}$ to 5; 12th (NCI), $1\frac{1}{5}$ to 2. Each kitchen is staffed to accomodate 10 patients, although 7 or 8 are considered the ideal workload. When the census falls below 6, the kitchen is over-staffed and employees, highly trained and of the highest calibre available for their type of work, have time on their hands. This situation, continuing over long periods of time, creates the additional problem of low morale in both professional and non-professional personnel.

The rearrangement of Heart Nursing Service units in the Clinical Center necessitated the construction on the 8th floor of a new metabolic kitchen and moving the 7th floor metabolic kitchen equipment and personnel to the 8th floor. Several serious mistakes in the new construction were made and emergency work requests for their correction had to be completed before the moving could take place.

The personnel cafeteria operation showed a deficit for fiscal year 1963 of $33,729. There may be some reduction in the amount of the deficit for fiscal year 1964 inasmuch as the pay raise has been offset by increased sales to some extent, and replacement of the stock of china and silverware was included in last year's expenses. However, because of long hours of service necessary 7 days a week for hospital staff and the high salary schedule of non-professional personnel, the deficit will continue, and recommendation has been made that the Nutrition Department be relieved of the Clinical Center personnel feeding responsibility.

GSA "choice" grade canned fruit has not met NIH standards this year. Revision of specifications to "fancy" grade has been recommended.

Shortage of classroom space for training becomes more acute each year. The 14th floor assembly room, the only space available to the Nutrition Department for training in the past 10 years, is now being used by another department. The Chief, Nutrition Department, has recommended that the terrace outside rooms 1S-217-221 be enclosed to provide classroom space for several departments.

III. ACCOMPLISHMENTS, CHANGES, AND IMPROVEMENTS

The services provided Clinical Center patients by the Nutrition Department cannot be truly perceived through the usual statistics; that is, numbers of rations served or categories of diets. Statistics do not reveal that many patients are too ill to eat their meals regularly, that before each meal they must be visited by Nutrition Department personnel and encouraged or coaxed to eat in order that their nutritional needs may be met. Nor do statistics show the patience and care needed to accomodate the food preferences and whims of many patients, or that diets must be changed or completely recalculated at times for the sake of the patient.

Increased interest in fluid balance and fluid intake was evidenced by requests of investigators for collection of this additional data in many studies. The number of 24-hour fluid intakes measured by the Nutrition Department in fiscal year 1963 increased by 11.8% over those recorded in 1962. Fiscal year 1964 seems to be keeping pace.

In fiscal year 1963, the Nutrition Department provided 377,231 patient meals; recorded 25,197 daily food intakes (an average of 69 a day); 14,925 fluid intakes (41 a day average); and weighed food on 151,182 individual trays (414 daily average). Individual discharge or follow-up diet instructions were given to 258 patients. In addition, to assist with the investigation of in-patients, complete nutrition histories were taken of 276 patients.

Twelve floor kitchens, a formula room, the main kitchen, and the 3-B (NCI) and 9th (NIAMD) metabolic kitchens were operated the full 12 months of fiscal year 1963. The 7th (NHI) and the 12th (NCI) were closed less than a month each. The 12th metabolic kitchen was discontinued on October 31, 1963.

Three metabolic conferences were conducted in fiscal year 1963, to train 9 dietitians from 9 institutions in the organization and operation of metabolic kitchen units for new medical research units supported by NIH grants. As of April 3, (fiscal year 1964) three metabolic conferences have been held. Seven dietitians from five institutions, as well as four dietitians from the Nutrition Department participated.

Patient Dietetic Service staff made a study of daily activities of the therapeutic dietitians in the Clinical Center. The report, "An Appraisal of the Daily Activities of the Therapeutic Dietitian in a Research Hospital," was written by Miss Jeanne Tillotson and Mrs. Maureen Loughney and was published in the Journal of The American Dietetic Association, October 1963.

At the request of Dr. William Zukel and Mr. Joseph Schachter, Laboratory of Technical Development, NHI, Miss Merme Bonnell, Metabolic Dietitian, Nutrition Department, was authorized to consult and assist with the evaluation of forms and data collected on the overall NHI dietary study evaluation. During April through December 17, 1963, Miss Bonnell contributed 259 hours to the study.

In April 1963, the Nutrition Department made a pilot study of methods of collecting data and means of control for a further study to be made for the purpose of establishing hot food temperature standards for hospital patient food service. Until the recent appearance on the market of the TRI R Electronic Thermometer, inadequate equipment for measuring temperatures was a major factor contributing to the scarcity of data on desirable food temperatures. This precision instrument was used in the study and permitted rapid and accurate collection of data with little interference in service. Foods classified as soups, meats, and vegetables, selected from the regular patient menu, were used in the

pilot study. Temperature readings were taken of each food item at five points of service. The study reaffirmed that the amount of exposed surface area in relation to the total quantity of food in a container, the consistency of the food, and the method of holding the food between preparation and service markedly affect temperatures. The Nutrition Department is evaluating these variables in order to establish controls and methods for continuation of the study.

A study of published literature relating to hospital formula units was also made by the Nutrition Department in order to evaluate and possibly improve the Clinical Center formula unit. Plant Engineering personnel cooperated and provided accurate measurements of room temperatures, humidity and lighting. Recommendations in published literature as well as those of Dr. Heinz F. Eichenwald, who studied the unit in May 1962, were compared with procedures, equipment and space of the Clinical Center formula unit. Eleven general recommendations for changes were submitted to the Associate Director, Clinical Center, for consideration.

Patient Dietetic Service staff compiled a new diet calculation book for use exclusively at the Clinical Center, and for the primary purpose of calculating routine calorie intakes. The book cannot be used for calculating constant or other controlled research diets.

An academic educational leave program for Nutrition Department professional staff has been approved. In January 1964, the Chief, Patient Dietetic Service, first to participate, began her year's work at the University of California School of Public Health to earn her Master's degree in Public Health.

The remodeling of dishwashing units of eight floor kitchens, begun in May 1963, was completed in April 1964.

Nutrition Department purchasing responsibility has increased greatly since the telephone charge order authorization in November 1962. In a 3-month period in fiscal year 1963, orders increased by $4300 over orders made for the same period in 1962.

To assist with this increased responsibility, a post-index card file was set up for the Nutrition Department Purchasing Unit to provide ready reference on each item of equipment, supplies and food purchased by 402, petty cash, or telephone charge order. Source of supply, date ordered, amount ordered, price, method of purchase, project number, specification and description are provided for each item.

IV. HONORS AND AWARDS

Miss Jeanne Reid, metabolic dietitian, presented her paper, "Thiamine Deficiency in Rabbits," at a meeting of the Federation of the American Societies for Experimental Biology, April 1963. Miss Reid was extended

acknowledgement in the following publications:

Buskirk, Elsworth R.; Thompson, Ronald H.; and Whedon, G. Donald: Metabolic Response to Cold Air in Men and Women in Relation to Total Body Fat Content. J. Applied Physiology 18: 603-612, 1963.

Lutwak, Leo; Laster, Leonard; Gitelman, Hillel J.; Fox, Maurice; Whedon, G. Donald; (with technical assistance of Dorothy E. Wolfe and Minnie L. Woodson): Effects of High Dietary Calcium and Phosphorus on Calcium, Phosphorus, Nitrogen and Fat Metabolism in Children. American Journal of Clinical Nutrition, Vol. 14, 76-82, Feb. 1964.

Miss Ernestina Bou was extended acknowledgement in the following publication:

Fredrickson, Donald S.; Ono, Katsuto; David, Louis L.: Lipolytic Activity of Post-Heparin Plasma in Hyperglyceridemia. Journal of Lipid Research, Vol. 4, No. 1 24-33, Jan. 1963.

Awards were given to two main kitchen employees at a Clinical Center staff meeting on January 15, 1963: Wardell Ross, for suggesting that a steam hose be installed in the bake shop; and William M. Mason, Assistant Kitchen Manager, for sustained superior work performance.

At a Nutrition Department awards assembly on June 27, 1963, Mrs. Mary B. Brown received a cash award for designing a container for butter.

V. PROPOSED FUTURE OBJECTIVES

A gradual replacement of all hot food carts used to transport food to the patient area is planned. New carts will be designed to keep hot a variety of foods in small quantities. A cart designed by the Nutrition Department was tested in November 1963, and was found satisfactory. New carts will be built along the lines of this one.

The food temperature study, aimed at establishing temperature standards for hot foods in a hospital food service, will be continued.

Metabolic conferences for metabolic dietitians opening new kitchens will be continued as the need arises.

The Nutrition Department Follow-Up Unit, activated as a pilot study in March 1963, will be converted from part-time duty to full-time to meet increased needs.

January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

ENVIRONMENTAL SANITATION CONTROL DEPARTMENT

CC-71
Serial No.

A. Program Goals

1. Provide the safest possible sanitary environment consistent with activities of the various Institutes and auxiliary services in the Clinical Center, buildings 10A and T-4.

2. Continue to study the manpower requirements of the Operations Section and formalize many of its work procedures.

3. Continue to orient, train, and supervise the Operations Section's personnel so that they are more proficient in carrying out the program objectives.

4. Continue to test various products and equipment to assure utilization of the most modern housekeeping practices.

5. Develop an organization to cope with day-to-day environmental problems within the Clinical Center and to study the overall environment as it relates to an institutional setting.

6. Make a special effort to complete the staffing of the Development and Training Section so it can reach its objectives.

7. Develop new training materials and programs that are consistent with the specific needs of the personnel for whom they will be used.

8. Make a concerted effort to provide "outside the Service" as well as "inside the Service" training opportunities for the professional and non-professional staff to enable them to keep abreast of the latest information in the bio-engineering and housekeeping fields.

9. Initiate an environmental evaluation program to maintain a day-to-day surveillance of the Clinical Center.

10. Obtain a higher quality of workmanship on job orders submitted by this department to other NIH divisions.

11. Have all electrical outlet receptacles in the Clinical Center grounded and all electrical equipment fitted with a 3 wire grounded cord.

12. Obtain agreement with the NIH authorities to use paints that are washable and suitable for a hospital and laboratory environment.

13. Obtain more adequate office space for the Operations Section and workshop space for the Development and Training Section.

14. Obtain adequate "one location" storage space in the Clinical Center so that all supplies and equipment for the Operations Section can be more adequately controlled and accounted for.

B. Progress Achieved

1. The Operations Section has noticeably stepped up its cleaning operations throughout the Clinical Center. This is partially due to a ceiling increase for budgeted positions, training of personnel, and standardizing certain cleaning procedures. The Institutes have been encouraged to use the cleaning services available in the Clinical Center and the increase in requests necessitated providing an extra telephone line in the Operations Section office to handle the calls and to handle the increased administrative workload of that office.

2. Crew cleaning has been used to a limited extent where it is considered a more efficient way of doing a large job of a repetitive nature. Example- all the egg crate light fixtures throughout the Clinical Center were cleaned by a 5-man crew using the new double wash tank designed for this cleaning operation.

3. Procedures and routines have been established for cleaning building 10A. We are responsible for all areas except the second floor and the individual surgical suite and interconnected areas on the fourth floor.

4. During the year more adequate equipment was purchased for the Operations Section. Major equipment consisted of 7 box trucks for transporting dry wastes, 4 wall washing machines, 6 large and 30 small stainless steel mopping units, 20 Microstat vacuum cleaners, 30 - 19" floor scrubbing and buffing machines, 7 combination scrubbing-vacuum machines, 1 light fixture washer, 350 feet of nylon dirt-stopping floor matting.

5. New products and equipment were evaluated on the job. Numerous floor finishes were tested, which resulted in finding improved floor finishing materials. The combination scrubbing-vacuum machines are being used in corridors or large open-space areas for daily maintenance and on snow days to pick up excessive water and salt accumulation at all entrances.

This prevents accidents from slippery floors and preserves floor finish thus reducing the need for frequent refinishing.

6. All Supervisors', Labor Leaders' and Office Personnel's job descriptions were revised.

7. A formal departmental promotion plan was established for wage board employees. All Laborers, Labor Leaders, and Supervisors were rated for a promotion panel. A total of 14 wage board and 6 GS employees were promoted by gradual assumption of duties, 13 wage board employees were promoted by selection from the Operations Section promotion panels, and 19 Supervisors were regraded upward by the revision of the Supervisory Standards for wage board employees in 1963.

8. Two hundred thirty-five applicants were interviewed and 108 applicants were hired by the Chief of the Operations Section. The "on the job" work record of each new employee was reviewed with him and his Supervisor 4 times for 2, 3, 6, and 9-month evaluations. This required approximately 242 hours of the time of the Chief of the Operations Section. Meetings were held with the Supervisors and Labor Leaders, and as needed with the full staff. Each employee received copies of new or revised personnel policies within the section.

9. An improved filing system has been established in the Operations Section office.

10. During the year one Supervisor received a Superior Work Performance Award.

11. A commissioned officer reported on duty in December 1963. At that time, the Development and Training Section began its functions to achieve the section's training goals.

12. The Development and Training Section conducted a general review of available literature to orient new staff members in the area of hospital environment. This introduction to the field was useful in supplementing the new staff member's engineering background. The Acting Chief of the section met with the environmental health staff of the University of Minnesota to become familiar with their work and educational program in the bio-engineering field.

13. A program to evaluate the environment of the Clinical Center has been initiated on a limited scale. Some information has been accumulated by the use of floor dirt sampling equipment.

14. Training materials from sources outside of the department have been located and reviewed. These materials will eventually be combined with the Development and Training and Operations Section's materials to provide a training manual for the Operations Section. A basic training course (in cooperation with the Clinical Center Personnel Officer and other NIH Employee Development Sections) has been presented to all supervisors of the Operations Section. This training course included 20 hours of class type discussion of the general areas of interest to all supervisors of the Operations Section. This year, major emphasis has been placed on supervisory training programs--on-the-job and formal. Training in emergency fire procedures, radiation safety and general safety procedures has been given to all members of the staff. Two supervisors were sent to Michigan State University to attend a 7-week Supervisory Training course in the elements of hospital housekeeping. A total number of 1663 hours for the calendar year 1963, and 2153 hours from January to June 1964, were spent on all training for a total of 3816 hours. See table 1 for a breakdown of all training activities.

15. The Development and Training Section in cooperation with the Operations Section has initiated limited evaluations of some of the supplies used within the department. A comparison of two germicidal detergents is being made and it appears that a new product may be suitable for use in the Clinical Center. The use of this new product would provide a government contract source of germicidal detergent at a significant savings to the Clinical Center.

16. A new type of liquid hand soap is being used in the Clinical Center. This change in product has reduced the cost of hand soap and provides a better product and better service than the previous product. Labor savings have been sizable (the new soap is more stable and does not spoil in the soap dispensers) and complaints have been eliminated. The Operations Section has "on the job" tested other cleaning products during the report period and some have been placed on our regular supply list.

17. The Development and Training Section has developed a procedure for the Operations Section to systematically clean drinking fountain bubbler heads in the Clinical Center. The drinking fountain heads have been removed, disassembled, delimed, cleaned and restored to use. It is believed that this is the first such type of cleaning that has been afforded these water fountains since the construction of the building. The fountain heads were heavily encrusted with lime which could not be removed by the regular daily cleaning procedures. An inplace routine cleaning procedure has been prepared by the section to maintain the cleanliness of the drinking fountains. This routine cleaning is now being accomplished by the Operations Section.

18. The Development and Training Section and the Operations Section are participating in the field trial of a paper bag refuse collection and disposal system on the tenth floor of the Clinical Center. If the system should prove to be effective, the Development and Training Section will prepare the training materials needed to assist the Operations Section during the change to the new system. The Development and Training Section is routinely reporting on the status of this test program.

19. An investigation is being made of ultrasonic cleaning equipment. It is felt that considerable labor savings may result when light fixture covers, venetian blinds, waste baskets, and many other small pieces of equipment are cleaned by ultrasonics.

20. A system is being developed to facilitate stairwell cleaning in the Clinical Center. The system requested would provide electrical outlets in the stairwells which would allow the Operations Section to use portable vacuum machines and possible light weight scrubbing equipment. These methods would improve the cleanliness of the stairwells but would keep the labor requirements at a minimum.

21. Floor matting is being tested at several locations in the Clinical Center. The primary locations are at the main entrance ways and on four elevators. Initial results indicate that the movement of a large amount of dirt is being stopped by the mats. The concentrating of the dirt on the mats enables the cleaning personnel to vacuum it up before it is spread throughout the building. This matting has enabled the reduction of floor stripping at elevator lobbies and first floor corridors and B-2 area from once a month or oftener, to once or twice a year.

22. Emergency calls and special cleaning. Emergency procedures have been set up to respond immediately and in an orderly manner to every general alarm. Wet-vacuum equipment has been set up and is always ready to respond to floods in the Clinical Center. On October 17, 1963 when a 4" water line, located in Room B1N-317, broke and flooded the B1N West area, 154.5 man-hours, regular time, and 34 man-hours, overtime were spent by the Operations Section to pick up the water with mops and vacuums or push it with large squeegees into floor drains. On October 25, 1963, Room 3N-256, after a fire was brought under control, 12 man-hours were spent to pick up the water. Numerous calls for non-routine services were received in the Operations Section and were responded to. During the month of January 1964, 1940 man-hours in the DSU and 374 man-hours in the NSU, were spent to meet all special and emergency demands. When the Heart Institute re-arranged their nursing units in December 1963 and January 1964, 563 man-hours, regular time, were necessary to general clean all areas.

C. Problems

There continue to be problems that we can solve by intradepartmental action; however, there are major problems that are beyond our control that require action and are the responsibilities of higher echelons. For example:

1. Equipment in corridors of the Clinical Center. Besides being a fire and accident hazard and presenting a very disorderly appearance, equipment in the corridors prevents proper cleaning of the floors, walls and ceilings. To efficiently use power equipment to clean corridors, it is necessary for the corridors to be clear. In addition to making it difficult to clean the corridors, the equipment stored there is subject to damage from the power cleaning equipment.

2. Personnel.

   a. During the reporting period, this department has not been fully staffed at any time. Personnel are available but the complex recruiting system and restrictions placed on hiring of laborers has made it impossible to hire quality people fast enough. Required use of the register system has prevented us from processing personnel efficiently and getting them on the job. Personnel considered undesirable for employment in the Clinical Center must be hired from time to time due to the one out of three rule. This hiring of undesirables increases the administrative workload of the Operations Section and all other along the line.

   b. The Veterans' Preference Act prevents this section from employing male custodial personnel who were not veterans prior to mid 1955. This generally prevents the hiring of personnel under 30 years of age.

   c. We were able to recruit some good caliber laborers during the past year, but have been able to retain only a few due to a 7-day-work schedule and to some extent, lower pay than other agencies and the distance NIH is from the area where most of our people live. Many of our good employees are recruited by the Institutes of NIH to work a Monday through Friday schedule. (See tables 2, 3 and 4.)

3. Materials selection. Problems arise in the cleanability and maintenance of various facilities and surfaces throughout the Clinical Center. Various surface materials and finishes have been specified without adequate consideration of the cleaning problems involved. The quality of materials and workmanship furnished as a result of work requests do not always meet the standards desired by this department. Many hours have been spent on these matters.

4. Space problems.

a. The Operations Section office is still marginal in its need for space using the NIH standard of 125' square per person. At the present time with 6 employees in rooms B1N-313 and 315, only about 82 feet is permitted per person. When properly staffed, it will be about 60 square feet per person, and a minimum of 400 additional square feet is needed. This does not take into account the space required for the employees to sign in and out.

b. The Development and Training Section is in need of workshop space of about 250 square feet - this is needed to do a minimum amount of laboratory, materials, and equipment testing in line with proposed environmental studies.

c. The Operations Section storage space is very poorly laid out. Supplies are stored in some 8 or 9 locations some of which cannot be locked. The amount of materials being stolen has not been determined at this time but a close inventory is now being maintained to attempt to determine any loss. (See tables 5 and 6.) The widely scattered space in store rooms from the 13th floor to the B-2 level should be consolidated - a minimum of 500 additional square feet is required to securely store equipment and supplies.

d. Space to start a small workshop which should be adjoining the main stock room is needed for minor maintenance and repair-oiling, greasing and cleaning of Operations Section equipment plus wheel chairs, stretchers and other small equipment items. Work that cannot be done on the nursing unit would be conducted here. About 250 square feet should be satisfactory for this operation at this time.

e. The Development and Training Section is limited by the number of personnel available and also by the facilities available to the section. At the time of this report, only one-third of the staff positions have been filled. The recruitment of personnel is limited by the shortage of trained candidates. All laboratory work which the department would like to have performed is currently requested from another division of NIH. This results in a need for close cooperation and communication between two separate organizations. Although the two organizations have been able to reach a harmonious working agreement at this time, it is anticipated that the laboratory workload will increase as the Development and Training Section completes its staff and expands the programs. It is anticipated that the expansion of the section programs will overload the laboratory facilities and place a stress upon the two cooperating organizations. The effectiveness of the section's program would be improved if the

section had the capability to perform the more routine laboratory work with section personnel in section facilities and farm out the more difficult work.

D. Plans for F.Y. 1965

1. Staffing - continue to urge the Clinical Center Personnel Office to maintain our labor and clerical staff at a maximum level. Recruit for an Assistant Chief for the Operations Section. Recruit for a Sanitarian or Engineer and clerical staff for the Development and Training Section to carry out desired environmental studies and implementations of the development and training materials and techniques.

2. Produce a manual for use in training personnel in the Operations Section to perform tasks in a uniform manner.

3. Continue to revise cleaning schedules for most efficient operations and adequate staffing requirements for proper coverage of all areas.

4. Study and develop methods for evaluating Clinical Center environment.

5. Continue to investigate new products and equipment that might improve the sanitation and appearance of the Clinical Center.

TABLE 1

TRAINING REPORT

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL

January 1, 1963 to June 30, 1964

Period January 1, 1963 to December 31, 1963

Course	Total Man Hours
Safety and Emergency Fire Procedures	460
Radiation Safety Procedures	172
Improved Mopping Techniques to Control Bacteria	145
Proper Operation and Maintenance of Floor Machines	147
Money Management Course	90
Basic Institute On Hospital Housekeeping	72
Operations Section Supervisory and Office Training	575
GS Personnel	2
Sub-Total Hours	1663

Period January 1, 1964 to June 30, 1964

Hospital Housekeeping Training Course, Lansing, Michigan	624
Supervisor Training Course, NIH	516
Special Refuse Collection, 10th Floor, CC	33
Operations Section Supervisory and Office Training	960
Business English Course	20
Sub-Total Hours	2153

Total January 1, 1963 to June 30, 1964 3816

TABLE 2

POSITIONS FILLED

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL

OPERATIONS SECTION

January 1963 through April 1964

MONTH	WB-4 and Above	WB-3	WB-2	WB-1	GS-2 and Above	TOTAL
January - 1963			7			7
February			4	1		5
March			7	2		9
April			7	1		8
May			7	1		8
June		3	12			15
Sub-Total		3	44	5		52
July - 1963		2	12			14
August	1	3	12			16
September		2	7			9
October		2	2			2
November						
December			5			5
Sub-Total	1	7	38			46
January - 1964			4		1	5
February						
March			3			3
April			2			2
Sub-Total			9		1	10
TOTAL	1	10	91	5	1	108

TABLE 3

NUMBER OF SEPARATIONS, RESIGNATIONS, ETC.

BY MONTH AND GRADE

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL
OPERATIONS SECTION

January 1963 through June 30, 1964

MONTH	WB-4 and Above	WB-3	WB-2	WB-1	GS-2 and Above	TOTAL
January - 1963		3	2	1		6
February		2	1			3
March		5	1			6
April			3			3
May		6	4			10
June	1	7	1			9
July		3	2			5
August		3	3			6
September		6	3			9
October		4	1		1	6
November			2	1		3
December		2				2
Sub-Total	1	41	23	2	1	68
January - 1964		2	2			4
February		2	4			6
March		3	1			4
April 14			1			1
Sub-Total		7	8			15
TOTAL	1	48	31	2	1	83

TABLE 4

REASON FOR PERSONNEL LEAVING

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL
OPERATIONS SECTION

January 1963 through December 1963

Resignations	Transfers	Retirement	Terminations	Deceased
7 Resigned when faced with possible disciplinary action or separation	3 Transportation	4 Retirement disability	4 Failure to report to duty	1
3 Drew retirement to pay debts	1 Better chance for promotion	2 Retirement		
3 Health	14 Higher pay; Monday-Friday; less travel			
2 To seek other employment or to accept non-Government position	17 Within NIH; Monday-Friday day only			
3 Moving away				
3 No reason				
2 To return to school				
Sub-Total 23	35	6	4	1
TOTAL - 69				

(Table 4 continued on next page)

Table 4 (continued) Reason for Personnel Leaving-Operations Section, DESC January 1, 1964 through April 1964

Resignations	Transfers	Retirement	Terminations	Deceased
3 Resigned when faced with possible disciplinary action or separation	4 Trans-portation	None	1 Failure to report to duty	None
	2 Better chance for pro-motion			
1 Health	2 Higher pay; Monday-Friday; less travel			
	2 Within NIH; Monday-Friday; day only			
Sub-Total 4	10	0	1	0
TOTAL 27				
Total leaving Operations Section for all reasons - 84				

TABLE 5

MATERIALS USED FOR MAINTENANCE OF SURFACES

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL
OPERATIONS SECTION

January 1963 through April 1964 (April estimated)

MATERIALS	1963 Jan. 1 thru Dec. 31, 1963	1964 Jan. 1 thru June 30, 1964	Jan. 1963 thru June 30, 1964
Germicidal Detergent	5500 Gal.	2016 Gal.	7516 Gal.
Speed Scope	4675 Gal.	1592 Gal.	6267 Gal.
General Detergent	4455 Gal.	2443 Gal.	6898 Gal.
Diversol	5240 Lbs.	1962 Lbs.	7202 Lbs.
Scouring Powder	1770 Lbs.	960 Lbs.	2730 Lbs.
Floor Finish	5225 Gal.	2079 Gal.	7304 Gal.
Hand Soap	2719 Gal.	820 Gal.	3539 Gal.

TABLE 6

MATERIALS USED

DEPARTMENT OF ENVIRONMENTAL SANITATION CONTROL
OPERATIONS SECTION

January 1964 through April 1964 (April estimated)

AMT.	UNIT	ITEM	AMT.	UNIT	ITEM
-	Ea.	Ash tray, glass insert	-	Gal.	Glamorene
322	Ea.	Ash tray, metal	337	Pr.	Glove, rubber: size____
-	Ea.	Ash tray, wood	-	Ea.	Mop, wet__oz.
190	Pkg.	Bag, paper, non-treated 40 lb.	305	Ea.	Pad, scouring, nylon
650	Pkg.	Bag, paper, treated	357	Ea.	Pad, steel wool:___",#___
165	Pkg.	Bag, polyethylene (large)	-	Pad	3M Pad____
57	Pkg.	Bag, polyethylene (small)	32	Btl.	Polish, furniture
14	Ea.	Broom, Floor sweep __inch	2	Gal.	Polish, stainless steel
33	Ea.	Brush, counter	640	Can	Powder, scouring
13	Ea.	Brush, nail	-	Ea.	Bags, paper wiping
7	Ea.	Brush, pot	-	Oz.	Shampoo, rug; Neo-Glo or equal
-	Ea.	Brush, pot, long handle	12437	Bar	Soap, Ivory, bar
10	Ea.	Brush, radiator	230	Ea.	Sponge, cellulose
473	Ea.	Brush, test tube	-	Ea.	Tag "Infectious Material"
-	Ea.	Brush, test tube (vents)	-	Roll	Tape; type___
570	Ea.	Brush, toilet	10714	Roll	Toilet tissue
28	Ea.	Dust pan	17600	Pkg.	Towel, paper, C-fold

Table 6 (continued) Materials Used, Operations Section, DESC

AMT.	UNIT	ITEM
-	Pkg.	Towel, paper, multi-fold
-	Ea.	Vacuum parts; type__
-	Gal.	Vinegar
1344	Gal.	Detergent, germicide
240	Pr.	Glove, work
23	Ea.	Handle, mop, size__
166	Btl.	Hand lotion
45	Ea.	Knife, scraping
21	Ea.	Mat, bath
18	Ea.	Mop, dust; size__
5	Btls.	Windex
57	Gal.	Airkem A-33
5 1/2	Gal.	Wall wash concentrate
1	Btl.	"Old English" scratch remover
3	Pkg.	Bags, sanitary napkin
51	Ea.	Furniture tip
458	Oz.	Tiara
1 1/2		Light shades
12	Oz.	Misto
5	Ea.	Vacuum bags
1628	Gal.	Detergent
1308	Lbs.	Diversol
1385	Gal.	Floor, finish "Triple Life"
546	Gal.	Soap, liquid, hand
1061	Gal.	Stripper
110	Gal.	Wash 'N Wear
4	Roll	Steel wool
2	Ea.	Baseboard brush
1	Ball	Twine
7	Ea.	Wastebasket, gray
3	Ea.	3M Pad
5	Lbs.	Sand
1	Ea.	Wire sponge
1	Can	Oil, 3 and 1
7	Ea.	Door silencer

January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

SUMMARY ANNUAL REPORT OF PROGRAM ACTIVITIES
CLINICAL CENTER

RADIATION SAFETY DEPARTMENT

CC-87
Serial No.

Mission

The Radiation Safety Department is responsible for all aspects of the proper usage, control, inspection, safeguard, and disposal of radioactive materials used at NIH. It is also the operating unit responsible for the Clinical Center low level counting facility (whole body gamma ray spectrometry for clinical investigation). Many of the department's safety and control functions are concerned with the use of diagnostic and therapeutic radiology and radioactive materials in patient care activities, and practically all of the research service activities of the low level counting facility involve patient care.

Developments and Trends

The use of radioactive isotopes at NIH has continued to increase at an essentially constant percentage. Figure 1 shows the number of shipments increasing at a rate which doubles the number every 3.3 years. The total activity received is no longer following an exponential growth curve, but seems to have stabilized at about 40 curies per year. This stabilization is probably due to three factors: the availability of more sensitive equipment for radioactive assays; the insistence of the Radiation Committee that the most sensitive assay equipment be used; and the widespread indoctrination programs in radiation safety carried out by the Radiation Safety Department.

The workload on the Radiation Safety Department is proportional to the number of shipments received rather than to the amount of activity involved. Under the requirements of our AEC license and NIH regulations, equal effort must be expended on a large or a small shipment. During this report period the Radiation Safety Department made over 2100 radioactive assays. More than 12,000 film badges were issued, processed, evaluated, and reported. Nearly 50 tons of radioactive wastes were processed for burial at sea under our cooperative arrangement with the Coast Guard. By June 30, 1964, 407 laboratory rooms contained radioactive materials at levels requiring periodic surveys under our AEC license requirement. More than 800 individuals are on the regular film badge service and about an equal number work with beta emitters only, where exposure can be estimated only by bio-assays of urine.

Major Accomplishments

During the reporting period 240 scientists completed the Department's intensive 2-week course leading to individual qualification for an AEC license. The course content and laboratory exercises were re-evaluated and substantially improved. In addition, a series of three lectures on radiation safety has been made available once each month to all new members of the nursing staff. Special classes were held for staff members of the Clinical Center's Department of Environmental Sanitation Control and the NIH Safety Branch's Guard and Fire Department.

Two new services have been provided to qualified isotope users. A tellurium generator is maintained at all times by the Radiation Safety Department from which 2.3 hour iodine-132 can be separated as required. There is a substantial reduction in radiation dose to the patient whenever clinical requirements permit the use of iodine-132 in place of the longer-lived iodine-131. A molybdenum-99 generator is also maintained to provide technetium-99 for clinical purposes. In both cases, the Radiation Safety Department assumes responsibility for the radiochemical purity of the product.

No personnel exposure approached the value of 5 roentgens per year presently considered an allowable occupational level. There were minor contaminating events, but no accident leading to an appreciable loss of laboratory equipment or building structure.

The human whole-body counter came into full-scale operation early in the report period. As operating experience was gained and calibration procedures developed, the counter was made available for a wider variety of assays of clinical interest. Determinations of body potassium have been requested most frequently. Assays involving radioactive iodine, iron, chromium, cobalt and calcium are also done regularly. In addition to its uses in clinical medicine, the counter has been a valuable adjunct to the Radiation Safety Department. All members of this group, and other NIH personnel working with substantial quantities of gamma emitters are counted routinely. These are supplemented by counts whenever there is a possibility of an overexposure to gamma emitters. During the last half of the report period more than 110 whole-body counts were being made each month. This represents a saturation value which cannot be greatly exceeded with the present equipment.

Publications

Andrews, H. L., Peterson, D. C.,and Jacobus, D. P.: Studies on the Effects of Chemical Protective Compounds In Mice at Low Radiation Dose-Rates. Accepted for publication in Radiation Research.

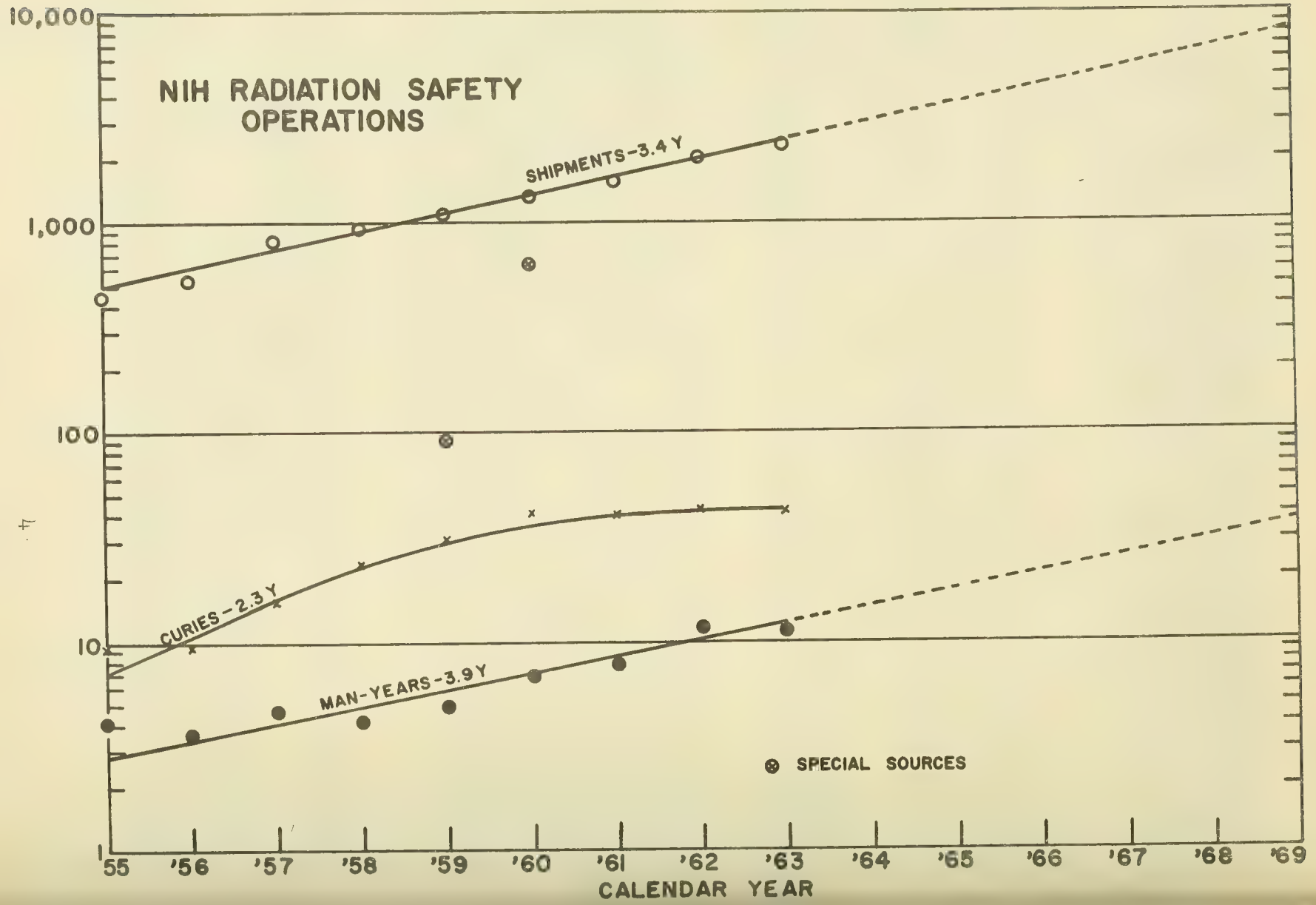
Brown, J. M.,Jr., Williams, K. D.: Monitoring and Assay Procedures for Krypton-85 Used in Circulatory Tests. To be published in Comptes Rendus.

Brown, J.M.,Jr.,Howley, J.R., McIntosh,Y.,Driver, D., and Dickinson, M.: Contamination Problems Associated with the Administration of Massive Doses of Sulfur-35 to Patients. Accepted for publication in Health Physics.

Future Plans

Efforts will continue to maintain the radiation exposures at NIH at the lowest possible levels consistent with the needs to use radioactive materials. The Department will probably supply an increasing fraction of the short-lived isotopes used at NIH. The clinical application of the whole-body counter will be extended and its isotope localizing abilities exploited.

Fig. 1 - NIH Radiation Safety Operations - Past and extrapolated. The figures beside each line indicate the time of doubling the corresponding activity.



ANNUAL REPORT OF PROGRAM ACTIVITIES

Division of Biologics Standards

January 1963 - June 1964

TABLE OF CONTENTS

ANNUAL REPORT
DIVISION OF BIOLOGICS STANDARDS

	Serial No.
Introduction and Summary	
Office of the Director	1
Experimental Virology	2
Experimental Virology (Papova viruses)	3
Experimental Virology (Adenovirus)	4
Experimental Virology (Miscellaneous viruses)	5
Pneumococci	6
Laboratory of Bacterial Products	
Pertussis Vaccine	7
Influence of Preservatives and other Factors on the Instability of Potency of Pertussis Vaccine	8
Investigations Concerning Sterility Testing	9
Studies on Cholera Vaccine	10
Immunologic Studies on Cholera in the Infant Rabbit	11
Comparative Studies of Recently Isolated Cholera Vibrios	12
Gastroenteritis Due to Noncholera Vibrios	13
Studies on the Specificity of Tuberculin	14
Properties of Dialyzable Tuberculins	15
Standardization of Poison Ivy Extracts	16
Toxicity and Sensitization Studies with Poison Ivy Extracts	17
The Schick Test Toxin (Diphtheria)	18
Investigation of Tetanus Toxoids for Prevention of Neonatorum Tetanus	19
A Study of the Antigenic Products of Various Strains of *Clostridium tetani*	20
Standardization of Reference Preparations for Tetanus Toxoids	21
Pleuropneumonia-like Organisms	22
Recurrent Aphthae	23
Bacterial Meningitis	24
Haemophilus Infections	25
In vitro Production of Sodium Pump Inhibitors by *Vibrio cholerae*	26
Laboratory of Biophysics and Biochemistry	
Studies of the Inactivation of Viruses	27
Physical Characterization of Biological Substances	28
Simian Virus 40. Electron Microscopic Studies of its Relationship to Rhesus Kidney Tissue Culture Cells	29

Development of Methods for the Chemical Analysis of Biological Products 30
Attempts to Cultivate Animal Viruses in Bacterial Cells 31
Genetic Variation in Bacteriophages 32
Physical and Chemical Characterization of Viruses 33

Laboratory of Blood and Blood Products

Preparation, Characterization, Stability and Potency of Blood Products 34
Report on other than Research Activities

Laboratory of Control Activities

Office of Chief 35
Investigations Related to the Establishment and Maintenance of Reference Standards for Biological Products 36
Section on Pyrogens 37
Control Testing and Investigations Related to Control of Biological Products 38

Laboratory of Viral Immunology

Neurovirulence Tests on Live Poliovirus Vaccines in Monkeys 39
Monkey Safety Test for Poliomyelitis Vaccine and Adenovirus Vaccine 40
Neurovirulence Tests on Measles Virus Vaccines in Monkeys 41
The Pathogenesis of Infectious Diseases 42
Immunological Studies of Attenuated and Virulent Polioviruses 43
In Vitro Tests on Live Poliovirus 44
Studies on Simian Virus$_{40}$ 45
Serologic Studies Concerning Poliomyelitis and Poliomyelitis Vaccines 46
Study of Inherited Metabolic Disorders in Human Diploid Cell Strains (HDCS) 47
Studies on Simian Viruses 48
Studies on SV$_{40}$ Virus, an Important Adventitious Agent of Rhesus Monkey Kidney Cell Cultures 49
Safety Testing of Killed Virus Vaccines in Cell Cultures 50
Occurrence of Pleuropneumonia-like Organisms in Serial Cell Cultures 51
Preparation of Primary and Serial Cell Cultures for Research and Vaccine Test Use 52

Laboratory of Virology and Rickettsiology

Administration, Research Planning and Coordination	53
Studies on Arthropod-Borne Viruses (Arboviruses)	54
Biologic Properties of the Sandfly Viruses	55
Studies on Virulence and Avirulence in Rickettsiae	56
Studies on a Possible Psittacosis-like Agent Isolated from Cercopithecus aethiops Tissue Culture Material	57
Biologic Studies on Resistance Inducing Factor (RIF) in Tissue Cultures	58
Development of Continuous Tissue Culture Lines for Use in Testing of Vaccines	59
General Aspects of Virology and Rickettsiology	60
Mechanisms of Intracellular Infection	61
Antigenic Studies of Epidemic Typhus Rickettsiae	62
Studies of Killed Epidemic Typhus Vaccine	63
Rickettsial Vaccines	64
Avian Leukosis Viruses in Relation to Human Vaccines	65
Studies Concerned with Respiratory Viruses	66
Studies Concerned with Virus Identification	67
Plaque Assay and Characterization of Inhibitor Resistant and Sensitive Variants of Influenza Virus	68
Investigations Concerned with Human Hepatitis Viruses	69
Studies on Antimicrobial Agents in Foodstuffs (Paolins)	70
Investigations Concerning Rubella Virus and Vaccine	71
Investigations Concerning the Smallpox Group of Viruses and Smallpox Vaccine	72
Investigations Concerning Measles Virus and Vaccine	73

Serial No. DBS 1

1. Office of the Director
2. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Program direction and administration for the Division of Biologics Standards is centered in the Office of the Director, with centralization of administrative procedures relating to personnel, travel, supply and accounting. Major objectives are determined and program responsibilities are assigned to the operating units within the Division. For each major area, staffing patterns are developed and are continually reevaluated in relation to program changes. The required financial support is determined for each area in relation to the Division's total budget. A major activity of the Office of the Director is the maintenance of the proper balance between the control activities and the research programs, the latter being supported to the degree that such investigations are required in order to meet the control responsibilities of the Division.

The Director working with members of his immediate staff, including a legal assistant, conducts a continuing review of existing regulations for the control of biological products, making revisions as necessary and also develops additional regulations as required for new products.

The Office of the Director includes a Section on Statistics and a Section on Experimental Virology.

During the reporting period two new activities were initiated within the Office of the Director. Those were (a) an office to handle the Investigative New Drug applications which began to be submitted to the Division of Biologics Standards when regulations concerning Investigations with New Drugs were adopted, and (b) an office of Scientific Information to cope with the Division's needs for current scientific information and to develop methods for systematizing and retaining information present in the voluminous Investigative New Drug and License applications which the Division receives.

Within the Office of the Director, the Information Office continues to be concerned with, (1) communications through such media as press, radio, television, publications and exhibits of information to the public on the Division's control and research activities, and (2) internal communication of such information through reports to the Director, NIH, and to the Surgeon General as well as to the Department and to the Congress.

Close and continuous liaison is maintained with technical representatives of industry. Frequent meetings are held between members of the Division's professional and administrative staff and individual manufacturers and groups of manufacturers who are concerned with common problems (these

occasionally take the form of conferences which also involve outside consultants to the Division). In addition, approximately 200 conferences are held each year with technical representatives of manufacturers who desire to discuss production and testing programs peculiar to their own organization.

The Office of the Director services the Board of Scientific Counselors, the Technical Committee on Poliomyelitis Vaccine, the Public Health Service Committee on Live Attenuated Poliomyelitis Vaccine, as well as numerous Ad Hoc Committees which are appointed from time to time to consider matters relating to the control of biological products.

Considerable effort continued to be devoted to enforcement activities in the blood and blood products field, and problems relating to the licensing of measles vaccines.

The resources of the Division continues to be heavily taxed by the growing workload. It has been possible to meet these increased demands by diverting personnel and resources from projects of lower priority and by postponing investigations in other areas. Increased support has been requested but full and efficient implementation of the support will only be possible when the planned additional facilities become available to the Division with the completion of the new building now estimated to be in 1966. Funds for construction have been appropriated, and it was originally planned that designs would be completed by November or December of 1963. However, despite a great deal of effort on the part of the Division of Biologics Standards and of the National Institutes of Health staff involved to meet deadlines, the architect has not completed the plans and it is doubtful whether construction will start before December 1964.

DIVISION OF BIOLOGICS STANDARDS

INTRODUCTION

The Division of Biologics Standards, which has the responsibility for administering the provisions of the Public Health Service Act with respect to the control of biological products, discharges this task as a blend of research and administrative activities which are about equally divided between control and research. The research programs are concerned largely with the basic function of the Division -- the control of biological products -- although by their very nature, some of these activities could well be classified as basic or fundamental research. However, no programs are undertaken initially unless they have direct bearing on the responsibilities of the Division. The activities of the Division -- both control and research -- are therefore product-oriented, and their scope, direction, and intensity are dictated by the need to provide essential information for developing requirements and regulations for the licensing and release of biological products. The Division research program is vital in this respect.

It is characteristic of the type of responsibility which the Division has, with its ultimate objective the protection of the public against unsafe and uneffective biological products, that the Division is confronted with a series of problems which are often never completely solvable. The successful accomplishments of the Division reside in those instances where difficulties are anticipated, headed off, or abated. It is necessary to maintain an active scientific interest in products which have long since been routinely accepted by the medical and health professions, and in some instances even forgotten by the majority of scientists working within the field. The Division can never move its area of interest completely or abandon a concern for any of the products which remain licensed. Smallpox vaccine is an excellent example.

During the period covered by the present report, the most notable events were perhaps those which affected the staff of the Division. The death of Dr. J. E. Smadel, who was Chief of the Laboratory of Virology and Rickettsiology, saddened everyone while at the same time depriving the Division of the services of one of the most widely known virologists in the world. Three of the senior members of the staff of the Division retired during this period. These were Dr. William G. Workman, Chief of the Laboratory of Control Activities, Dr. George A. Hottle, Chief of the Laboratory of Viral Immunology, and Dr. Thomas H. Tomlinson, Jr., Assistant Director of the Division. The Division was, however, fortunate in being able to secure the services of Dr. Alexis I. Shelokov, who was appointed Chief of the Laboratory of Virology and Rickettsiology. Dr. John T. Tripp, formerly Chief of the Laboratory of Blood and Blood Products, was appointed Assistant Director of the Division. In anticipation of the ultimate formalization of certain organizational changes directed at the better functioning of the Division, the section on Pathology of the Laboratory of Viral Immunology under Dr. Ruth L. Kirschstein reports to the Director. The Laboratory of Viral Immunology and the Laboratory of Virology and Rickettsiology interchanged a section each (The Tissue Culture Section is now in LVR and the General Virology Section is now in LVI). Dr. Harry M. Meyer, Jr., is Acting

Chief of the Laboratory of Viral Immunology and Dr. John N. Ashworth is Acting Chief of the Laboratory of Blood and Blood Products. Dr. John C. Wagne of the Director's staff has been designated Acting Chief of the Laboratory of Control Activities. With these changes, the Division is continuing to carry out its dual function of control and research satisfactorily.

Regulations governing clinical investigations with new drugs became effective during the early part of 1963. In the case of biological products, it is now necessary for those engaged in clinical investigation to comply with the provisions of §130.3 of the Food and Drug Regulations and submit "Notices of Claimed Investigational Exemption for a New Drug" to the Division of Biologics Standards. To meet the demands of these new requirements, a separate activity has been set up within the Office of the Director, DBS. This is headed by Dr. Helen L. Tepper. It should be pointed out that this type of activity has been carried out by the Division on a less formal basis for a great many years. Because Regulations or to use the statutory word "standards" must be in existence before a biological product can be licensed, the Division must keep in close contact with those who are carrying out field and other investigations concerning the safety and potency of products so that the formulation of regulations or standards can be accomplished against a sound background of knowledge and experience. However, the new regulations prescribe the way in which the information being derived from clinical trials must be reported necessitating the development of a separate activity on Investigative New Drugs. As of June 30, 1964, the number of such submissions made to the Division was 93. The initial response of investigators to the new regulations was unfavorable. While there are still complaints about excessive paper work, we believe that most now feel that while the system will undoubtedly improve with time, it does protect the interests of the investigator and of the patient or subject. Most of the difficulties which have been encountered have been with a too literal reading of the provisions of the regulations.

Live poliovirus vaccine continues to be used on a wide scale in the United States. This perhaps accounts for the exceptionally low rates of occurrence of poliomyelitis in this country during the summer of 1964. Only 42 cases had been reported up to June 30 as against 82 for the corresponding period in 1963. Epidemiologic information continues to indicate that the situation presented in the Report of the Surgeon General in December 1962 still persists. This report in effect stated that there was a minute hazard in the use of the type 3 strain. Thus the control of the vaccine continues to call for special vigilance.

A trivalent live polio vaccine was licensed in June of 1963. This is a satisfactory immunizing agent but its availability has given rise to misunderstanding on the part of users as to the merits of one vaccine in comparison with another. Properly administered, monovalent and trivalent vaccines are equivalent and effective immunizing agents. However, when monovalents are used a record must be kept of the particular type administere and this must be done on 3 occasions. With trivalent, a single preparation is used and this is given on two occasions spaced 8 weeks apart. Thus the procedure is simpler and attractive to some despite the slightly higher cost.

Two different kinds of measles vaccine were licensed in early 1963. One was a live measles vaccine using the Enders strain. The other form was an inactivated vaccine also using the Enders strain. Licensing was preceded by widespread public interest including a national television program in which members of the DBS staff participated together with others from the Public Health Service. Experience with live measles vaccine since licensing has been satisfactory and by the end of June, it was estimated that approximately 5 million doses had been administered in the United States with no serious side effects. Because antibody levels decline rapidly, results with the inactivated vaccine have not been considered favorable. Field results indicate that a dual approach may be desirable in avoiding the mild side reactions encountered with the live vaccine; i.e., inactivated vaccine followed some time later by live vaccine.

As indicated in the individual project reports, the West African studies under Dr. Harry M. Meyer, Jr., have contributed greatly to our understanding of immunization against measles and have shown the way to control a very important cause of childhood mortality in tropical regions.

Investigation of alleged violations of the "Biologics Law" continue to be demanding of the time of Division personnel. The time involved, and attention to detail in the collection of evidence which will stand up in court, requires that those involved devote most of their time to this activity. Accordingly, an investigation group is being organized under the Assistant Director of the Division. During the early part of 1963, three of the cases mentioned in the last report and which involved blood and plasma were brought to the point of decision. Judgments were handed down against the defendants in these three cases. These actions reflected great credit on the members of the staff of the Division who participated in the investigations which led up to the convictions. These judgments should have a salutory effect on any operators who wish to short-cut the safety and potency requirements of the statute and the regulations. However, the number of cases under current investigation would seem to indicate that the message has not been widely received!

The Division has held a number of symposia involving interested scientists and members of industry. Two which should be mentioned particularly were a Pertussis Vaccine Symposium held on October 21 and 22, 1963, and a Symposium on Rubella held on April 30 and May 1, 1964. Both aroused great interest and the proceedings have been transcribed for the purpose of making the information presented more useful. Another important and rather complex series of meetings were held between consultants and staff members of the Division of Biologics Standards and the Food and Drug Administration on the subject of oil adjuvants used with experimental vaccines and preparations for use in the treatment of allergic states. A report covering the recommendations of this group is expected.

The new addition to the facilities of the Division of Biologics Standards, Building 29-A, was still in the design stage by the end of the period covered by this report. The reasons for the delay are not clear but are of an administrative nature involving the architect and the General Services Administration. It is difficult for the scientific staff of DBS

who are working under over-crowded conditions to understand why the date for completion of design which was originally set for late 1963 should now be late 1964.

The following summaries of the programs of each of the laboratories present more details of the activities of the division.

LABORATORY OF BACTERIAL PRODUCTS

During the past 18 months while continuing the projects of the previous year, the Laboratory of Bacterial Products has placed special emphasis on the relation of laboratory evaluated potency to efficacy in man and has actively participated in three conferences on subjects directly related to the programs of the LBP.

Correlation of Laboratory Evaluated Potency of U.S. Reference Preparations with Human Response. Some years ago it was shown that mouse protective potency of pertussis vaccine was directly correlated with protection of children against whooping cough. The potencies of the field trial vaccines (British) were related to the U.S. Standard Pertussis Vaccine and the latter became the basis of reference for the establishment of the potency of the international standard. By request LBP is selecting a replacement for the first international standard pertussis vaccine. Potency again will be established in relation to the Master U.S. Standard.

Recently, in the laboratory evaluation of two typhoid vaccines, which in WHO sponsored field trials were found to afford significant protection, the U.S. reference typhoid vaccine was found to be inferior to either the acetone-killed-dried (AKD) or the heat-killed phenolized vaccine. Since the former was superior, an AKD vaccine has been procured by the Section on Reference Standards, LCA. The Section on Bacterial Vaccines is collaborating in the evaluation of the new preparation in relation to the field trial AKD vaccine.

The collaborative study on tetanus antitoxin response of pregnant women in Territory of Papua and New Guinea is providing valuable information relative to the laboratory evaluation of potency of tetanus toxoids. The laboratory potency of certain of the field trial toxoids are being compared with the international reference tetanus toxoid, plain, and the proposed international tetanus toxoid, adsorbed, as well as with the U.S. reference preparations.

Although in use many years, cholera vaccine has not been shown in controlled field trials to be efficacious in protecting man against cholera. Currently a trial is being carried out by the Pakistan-Cholera Research Laboratory, Dacca. Laboratory potency of the field trial vaccine has been related to the proposed U.S. reference vaccine by means of a revised potency test (SBV).

Studies on the relation of laboratory potency of vaccines to efficacy in man have been recognized by a Superior Service Award to the Chief of the Laboratory.

U.S. Standards of potency for allergens have not been developed. Emphasis is being placed on development of a standard for poison ivy extract by the Section on Allergens. About 80% of the people in the U.S. are sensitive to poison ivy and contact dermatitis is a significant occupational hazard. Catechol content as determined by gas chromatography and guinea pig skin reactivity were found to be directly correlated. However, when tested on man, it was found that pentadecylcatechol was only one-tenth as active as the extract on certain subjects. Further work has been initiated to relate synthesized catechols to human skin reactivity and also to determine if indeed man can be desensitized with poison ivy extract.

Conferences. (1) The Section on Bacterial Vaccines organized a symposium on pertussis vaccine which was sponsored by the DBS and held at the NIH in October to discuss problems relating to the manufacture and control of the vaccine and untoward reactivity in children. An outgrowth of the meeting will be an investigation to relate pertussis vaccine reactivity in children to laboratory measured toxicity.

Two staff members, respectively, participated in two Round Table Conferences of the International Association of Microbiological Societies, Permanent Section of Microbiological Standardization, London, England. (2) At the Conference on Sterility Testing, Dr. Pittman presented a general paper on culture media and temperatures of incubation and another paper in which were given the results of the current sterility testing study by Mrs. Cox, Section on Bacterial Vaccines. Much progress was made in coming to an international agreement on the use of one medium and one temperature of incubation for the general sterility test and the use of additional procedures for specific products. (3) At the Round Table Conference on Tuberculin, Dr. Baer, Section on Allergenic Products, presented the recent new and significant finding by him and Dr. Chaparas that a carbohydrate fraction of tuberculin can induce delayed skin reactions.

Tuberculin. In their comprehensive studies on the characterization of fractions of tuberculin, Doctors Chaparas and Baer, SAP, in addition to the finding mentioned above, have shown that skin reactivity is associated with dialyzable and nondialyzable components and that the substances with greatest immunological activity dialyzed slowest and had the greatest sedimentation constants.

Poison Ivy Extract. Doctors Bowser and Baer, SAP, in their studies directed toward a U.S. Standard of potency of this extract found when guinea pigs were injected or fed pentadecylcatechol in vegetable oil that immunological unresponsiveness was induced. However, when the same solutions were mixed with mycobacteria and injected or applied to the skin, skin sensitivity was induced.

Rhesus monkeys failed to develop contact dermatitis to poison ivy.

Tetanus Toxoid. In the collaborative study of the Section on Bacterial Toxins on the prevention of neonatal tetanus in the Territory of Papua and New Guinea, it has been shown that the mean antitoxin response to one injection

of toxoids in oil was significantly greater than the response to two injections of $AlPO_4$ adsorbed toxoid, and the latter was significantly better than the response to three injections of plain toxoid. There is promise that in those countries where the rate of neonatal tetanus is high, women of child-bearing age could be successfully vaccinated with one injection of tetanus toxoid in oil.

Dr. Hardegree, SBT, in her study on the separation of antigenic components of cultural filtrates of Clostridium tetani has obtained partial separation of neurotoxin and hemolysin.

Pleuropneumonia-like Organisms. Dr. Barile, SBT, in collaboration with Dr. Shimke (NIAMD) has described a rapid chemical method for the detection of PPLO contamination in tissue cell cultures in which arginine is converted to ornithine by arginine deiminase which is present in the contaminated cultures but absent in noncontaminated cultures. The test is proving to be very helpful in the screening of tissue cultures for contamination. In his collaboratory work with Dr. Graykowski (NIDR) pure cultures of a transitional L-form were isolated repeatedly from lesions in recurrent aphthae patients.

Pertussis Vaccine. Mrs. Gardner, Section on Bacterial Vaccines, has shown that the preservative benzethonium chloride which was used in the quadruple antigen product in place of Merthiolate to prevent deleterious effect of mercury on potency of poliomyelitis vaccine, was the principle cause of loss of potency of pertussis vaccine in the combined product. A mixture of methyl- and propyl-p-hydroxybenzoate, a commonly used preservative in pharmaceutical products was found to be also harmful to pertussis vaccine. In the presence of tissue culture, with or without polio virus there was slight, but not significant, decrease in potency of pertussis vaccine with time.

Since the revision in the toxicity test for pertussis vaccine two and a half years ago, there has been an overall decrease in the mouse toxicity of the lots of pertussis vaccine submitted for release. Graded dose-response curves prepared by Mrs. Cox, SBV, show that the lots would meet the requirement at a higher dose level than specified. An analysis of the toxicity tests performed by SBV over a 9.5 year period showed a remarkable consistency with a trend towards decreased toxicity.

Typhoid Vaccine. Additional experiments have confirmed the findings of 1962, that by the intraperitoneal route and not by the subcutaneous route of vaccination can the difference in human protective response be measured in a mouse assay. The manufacturers of typhoid vaccine have been notified of the superiority of AKD vaccine. A reference AKD vaccine has been procured by Sections Reference Standards, LCA, and SBV is collaborating in its potency evaluation in terms of the field trial AKD vaccine.

Cholera Vaccine and Cholera Vibrios. The maximum dose of a cholera vaccine that does not cause a delayed reaction in man has been related to mouse toxicity and nitrogen content. These observations formed the basis for a revision in the bacterial content requirements for cholera vaccine. Other information obtained on cholera vaccine should permit the issuing of a complete revision of the requirements for cholera vaccine in the near future

The recent spread of cholera to many countries in the Far East by vibrios that have some characteristics different from those that are the cause of endemic cholera in the Bengal area has stimulated much interest in the taxonomic characteristic of the cholera vibrios, their relation to epidemiology and efficacy of cholera vaccine. Dr. Feeley, SBV, is studying the characteristics of these epidemic strains and also the characteristics of non-cholera vibrios that are the cause of or are closely associated with an acute gastroenteritis.

Doctors Feeley and McIntyre, SBP, using the infant rabbit model to observe passive protection against experimental cholera have found that differences in protective activity are not necessarily reflected by in vitro measured antibody titers. Recently, Dr. Feeley has observed that protection is better with the lower molecular weight antibody than with the larger molecular weight antibody. The studies hold promise of a better understanding of the immune response to cholera vaccine and indirectly to the control of the quality of cholera vaccine.

Dr. J. Spaun, Visiting Scientist, is studying the factors of the cholera vibrio which affect the sodium permeability of the frog skin. The massive diarrhea of cholera is apparently due to disturbance of the sodium pump of the gut.

The Chief, LBP, is serving on the NIH Cholera Advisory Committee, the Pakistan-SEATO Cholera Research Laboratory Technical Advisory Committee, and as NIH Project Officer for the CRL.

Non-research Activities. During the period of January 1 to December 31, 1963, 597 tests were performed. These were for the control of pertussis vaccine, anti-pertussis serum and Haemophilus influenzae therapeutic and diagnostic sera.

Other regulatory activities consist of (1) submission of a proposed final draft of Additional Standards: Pertussis Vaccine for Proposed Rule Making Publication, and (2) participation in the review of license applications to determine eligibility of establishments and of individual products for license, inspection of establishments and liaison activities between the Division and one manufacturer of poliomyelitis vaccine.

LABORATORY OF BIOPHYSICS AND BIOCHEMISTRY

A major undertaking during 1963 was the establishment of a unit within the Laboratory of Biophysics and Biochemistry to provide for a systematic program of chemical analysis of biological products. This group, which is under the supervision of Dr. Jerome J. Helprin, consists of four chemists and occupies three laboratory modules. The function of the group is to perform chemical and physical analyses of licensed biologicals, products under development, and materials of research, as well as to conduct research in the development of methods and in the correlation of chemical composition with biological properties.

The long-range research program of the laboratory, identified primarily with the application of physical principles to microbiological systems, has continued at a reduced pace because of the reassignment of space and loss of personnel. Dr. John M. Easton completed an intensive study of the multiplication of SV_{40} in rhesus kidney cells. Dr. Nobuto Yamamoto, whose appointment as visiting investigator terminated in October 1963, contributed some interesting information on bacteriophage genetics prior to leaving NIH to join the staff of the Fels Research Institute at Temple University. Miss Dorothy E. Moore, who had carried out many of the virological experiments, left to extend her graduate study at the University of Chicago. Reorganization of the research program of the laboratory to match the personnel and space now available will be an important responsibility in the forthcoming year.

LABORATORY OF BLOOD AND BLOOD PRODUCTS

Summary of Research Activities. The research program of the Laboratory of Blood and Blood Products has included studies of the stability of blood products, as well as methods and standards for these products, blood banking equipment, red cell antigens and plasma antibodies, the clotting and fibrinolytic systems, and the proteins of body fluids. These various fields of interest have as their goal the improvement of procedures used for the control of the purity, potency and safety of biological products derived from blood. Thus the projects are directed not only toward improving existing control tests and developing new ones, but also toward providing stability data leading to more realistic dating periods for such products.

Studies of the stability of both Normal Serum Albumin (Human) and human gamma globulin during storage have been carried out. Information derived from the latter study has already been used in the preparation of Additional Standards for Measles Immune Globulin (Human) and has been considered in writing the initial drafts of Technical Standards for Poliomyelitis Immune Globulin (Human) and Immune Serum Globulin (Human).

Investigations of blood clotting have dealt with several phases of this complex biochemical process. In the course of this work a procedure has been developed for preparing plasminogen-free human fibrinogen that is also free of the fibrin stabilizing factor and/or plasminogen-free human fibrinogen that is also free of both the fibrin stabilizing factor and a plasmin (fibrinolysin) inhibitor which is present to varying extents in all human fibrinogen samples. The latter preparation is of interest as a substrate in plasmin testing since plasminogen-free, inhibitor-free fibrinogen exhibits a constant sensitivity to plasmin, whereas the sensitivity of other fibrinogen varies from batch to batch.

Summary of "Extramural" Research and Other Activities. The "extramural" program of the Laboratory is not formally organized in the sense of extramural programs of other Institutes. However, the nature of the control functions provides opportunities for numerous contacts with scientific staffs of outside organizations. For example, the Fourth Voluntary Blood Bank Evaluation has just been completed. Under this program participating laboratories perform

extensive tests on replicate samples of blood and report their results. Of the 202 establishments licensed for Whole Blood (Human), 179 participated in this evaluation.

The primary function of the Laboratory is the control of the purity, potency and safety of blood and blood products. Approximately three-fourths of the total time of the Laboratory personnel is occupied by this function. Control activities include the inspection of licensed establishments, the investigation of possible violations of the Public Health Service Act, and the testing of samples of blood products submitted for release, licensure, or as a result of inspections. The review of license applications, labels, and circulars and the development of Technical Standards for biological products prepared from blood constitute integral parts of the overall control activity. In support of these functions the Laboratory has conducted an Inspector Training Course.

To supplement the research activities of the Laboratory and yield specific information necessary for the development of regulatory standards, five research contracts have been negotiated. The project titles of these five contracts are:

1) Hemagglutinin Levels of Normal Human Plasma.

2) a) Optimal Standards of Potency for ABO Blood Grouping Serums.

   b) Development of Standards for Anti-Human Serum to Detect ABO Sensitization.

3) Anti-Human Protein Serums for Specific Identification of Proteins by Diffusion Methods.

4) Reagent Red Blood Cell Reference Panel.

5) Laboratory Studies of the Purity of Plasma and Plasma Fractions Stored in Plastic Containers.

LABORATORY OF CONTROL ACTIVITIES

This laboratory is responsible for activities dealing directly with licensed establishments in relation to the licensing and control of biological products. It is supported by sections on control tests, pyrogens, and reference standards.

Its activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physical facilities for manufacturing and testing of products, the scientific and professional qualifications of personnel and the evidence developed by manufacturers and the Division of continued safety, purity, and potency of products, for which an application for license is being evaluated. License applications are reviewed individually when required by an ad hoc committee consisting of appropriate members of the staff of the Division.

(b) Supervision of annual and special inspections of licensed establishments and of those for which an application for license has been made.

(c) Releasing of individual lots of biological products for distributi by manufacturers on the basis of review of manufacturers' and of DBS tests and of any other available information relating to the safety, purity, and potency of the lot of the product.

(d) The establishment and distribution of physical biological standard reference preparations, and control materials. A small culture collection is also maintained mainly for the Division and for licensed manufacturers.

(e) Review of requirements and regulations now in effect for such constructive revision as needed and the development of requirements and regulations for new products.

(f) Maintenance of close working relations with other laboratories of the Division and other agencies to insure continuous knowledge of information needed for the licensing of establishments and new products and for the testing, release, and control of products already licensed.

The scope of activities carried out by this Laboratory is indicated by the fact that during the twelve month period, January 1, 1963 - December 31, 1963 a total of 7,248 control tests were carried out to insure the sterili safety, potency and purity of licensed biological products as follows:

Products for Release	6,146	tests
Inspection Samples	1,038	"
Complaint Investigations..	64	"
Total	7,248	"

The results served as a basis for the release or rejection of individua lots of products. In addition 1,388 cooperative service tests were done on biological products not licensed.

During the same period 4,850 lots of biological products were submitted for release by licensed manufacturers. Of these 4,737 lots were released, 49 lots were rejected and 64 lots were withdrawn from consideration for releas by the manufacturer.

To maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing, it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were: antitoxins - 14, serums - 3, vaccines - 2, toxoids - 2. A total of 708 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests and a number of specialized tests for specific products.

Standards, reference preparations, and cultures are freeze-dried for greater stability during storage. The following were dried between January 1, 1963 and December 31, 1963.

Cultures	4,232	Ampoules
Serums	118	"
Vaccines	3,205	"
Viruses	1,295	"
Total	8,850	"

Official standards, reference, and control preparations currently maintained include 80 items.

Standards, reference preparations, and cultures were distributed to research or control laboratories of licensed and other manufacturers, health departments, and universities in this country and abroad as follows:

Antitoxins	378
Serums	2,761
Vaccines	931
Toxins	298
Bacterial & Viral Cultures	1,584
Total	5,952

LABORATORY OF VIRAL IMMUNOLOGY

During the eighteen months covered by this report the Sections comprising the reorganized Laboratory of Viral Immunology have maintained an active research program in vaccine-related fields and shouldered major responsibilities in the control of new biologic products.

Measles. The major effort of the Section on General Virology over the past several years has been devoted to acquiring information that would be useful in the development of live, attenuated and inactivated vaccines against measles. The first of these products was licensed in March, 1963 and there has now been over a year of general clinical use of both the live and "killed" vaccines. The Section has participated in a series of West African studies during which many questions relating to field use of the Enders "B" level attenuated strain have been resolved. These investigations involving vaccination of about one million children provided data which were extremely helpful in formulating the final requirements for the license of the live vaccine. Laboratory studies by the Section established standard methods for testing measles vaccines. The smooth transition from the period of research to license and subsequent general use of these vaccines testifies to the effectiveness of the Section in anticipating and meeting its research and control responsibilities in the measles field.

Rubella. Since the original reports of the isolation of rubella virus some two years ago a number of university and pharmaceutical groups have engaged in research activities that could ultimately lead to the development of vaccines. This past year the Section on General Virology responded to this general kindling of scientific interest by initiating a rubella research program as a major effort of the Section. Following the pattern set in the development of measles vaccines, the Division sponsored its first Conference on Rubella in April, 1964.

Smallpox. Smallpox continues to be a major health problem in much of the world and promises to be a constant threat to the United States and other smallpox-free areas for years to come. Maintaining an active smallpox research program, the Section on General Virology engaged in three clinical studies in the Republic of Upper Volta. This work provided information relating to the potency of vaccine in man as compared to several laboratory assay systems and data pertaining to jet inoculation of combined live smallpox, measles and yellow fever vaccines. These studies have opened several other promising avenues for exploration in the field of smallpox immunology.

Poliomyelitis. The Section on Viral Genetics has continued its research in the area of intratypic differentiation of poliovirus strains. This work and the application of "t" and "d" marker tests are extremely important in increasing our ability to predict by *in vitro* evaluation the *in vivo* performance of various strains of attenuated polioviruses. These techniques apply directly to characterizing the virus strains incorporated in live vaccines and experimental strains that may be candidates for vaccine manufacture. Pursuing this approach, it may ultimately be possible to determine the specific chemical basis of virulence in polioviruses.

The Section on Serology has maintained a program of poliomyelitis research and control. New reference standards of poliomyelitis immune globulin and poliomyelitis hyper-immune serum have been assayed for neutralizing antibody content and made available as standard reagents. The research effort of the Section has centered on developing new and improved methods for testing the potency of inactivated poliomyelitis vaccines and poliomyelitis immune globulins. This work has been essential to the Division in meeting responsibilities in the control of poliomyelitis vaccine and globulin.

Latent virus studies. Since the discovery of SV_{40} in 1960 it has become clear that many, if not all mammalian and avian species harbor latent viruses, some of which may have an oncogenic potential. The complexities of this problem are enormous but of obvious importance in the field of biologics control since most virus vaccines are produced in mammalian or chick embryo cultures or in embryonated eggs. The Section on Viral Genetics has been engaged in a series of basic studies pertaining to viral latency using SV_{40} as the model agent. The results to date have made a valuable contribution to our knowledge of the mechanisms of viral latency and viral-induced malignant transformation of cells.

Study of genetic defects at the cellular level. With the increasing availability of diploid cell lines and developing interest in their use for vaccine production, there has been a corresponding accentuation in basic research programs using diploid cells. The Section on Serology has used this tool to demonstrate that the metabolic defect of Niemann-Pick disease exists on a cellular level and can be demonstrated in diploid cell cultures derived from patients. This type of investigation may provide a useful approach to the study of genetic influence upon cellular metabolism.

Administrative Aspects. In December 1963, Dr. Alexis Shelokov was appointed Chief of the Laboratory to fill the vacancy resulting from Dr. Joseph E. Smadel's death in July 1963.

Preliminary functional changes in line with the planned reorganization have taken place: the Section on General Virology is being transferred to the Laboratory of Viral Immunology, while the Tissue Culture Section of LVI is being transferred to this Laboratory. A redefinition of the other Sections within LVR is also planned.

The Pakistan project and Mrs. Doris Parkinson, Special Assistant for this project, were transferred to the Office of International Research in November 1963.

Dr. S. Martin Harwin joined DBS in July 1963. Dr. Nicola M. Tauraso transferred to DBS with Dr. Shelokov from the Laboratory of Tropical Virology of NIAID. Dr. Mahmet Saglam, a Turkish Army Officer from Ankara, Turkey has been with the Section on Respiratory Viruses since February 1, 1963.

Miss Elizabeth Jackson of the Section on Basic Virology and Rickettsiology resigned in March 1964 to join the staff of the University of Maryland School of Medicine. Dr. Motoichi Hatano and Dr. Seiya Kohno completed their professional visits with the Division and returned to Japan in December 1963 and January 1964, respectively.

Rickettsiae. Rickettsial studies were continued during this reporting period. A most exciting finding was that microorganisms other than viruses can induce interferon production. A rickettsial interferon was induced by R. tsutsugamushi; it will be important to determine if other rickettsiae induce interferon and what role interferon plays in rickettsial infections in vivo.

Other projects concerned the development of a stable and potent killed epidemic typhus vaccine and a reevaluation of the present immunization schedule. The typhus rickettsiae in the infectious egg material were fractionated and the antigenicity and immunogenicity of these fractions were examined in an attempt to prepare purified antigens.

Influenza. With but a few other groups in this country, this laboratory continues to be concerned with the pathogenesis and immunogenesis of influenza; carefully designed human volunteer studies to elucidate these problems are in progress in collaboration with Laboratory of Clinical Investigations, NIAID.

A better system for the determination of the CCA content of influenza virus vaccines is under development in cooperation with the Auto Analyzer instrument of the Technicon Company.

A simple cell culture plaque assay method for influenza virus was developed; inhibitor-resistant and inhibitor-sensitive particles of the A2/305 prototype virus may differ in their antigenicity, a finding of possible future importance in the development of more potent vaccines.

Adenovirus Vaccines. Studies on the variables in the potency assay of formalin-inactivated trivalent adenovirus vaccines, defined the parameters of (1) number of immunizing injections, (2) response of monotypic component and the combination of these and (3) virus inhibitors in the sera of test animals before immunization.

Antibodies Against Simian Viruses in Human Sera. The prevalence of virus neutralizing substances against monkey adenovirus SV_{20} and monkey myxovirus SV_5 was determined in sera from 102 infants, children and adults living in two markedly different sociologic and ecologic settings (New Guinea and the United States). The results suggest the possibility that SV_5 and SV_{20}, or agents antigenically related to them, might be infectious for man.

Human Hepatitis Viruses. The general properties of the A-1 virus were previously reported. A significant development was the demonstration of neutralizing antibody changes in the sera from documented cases of hepatitis; of particular interest were seven individuals from New Jersey who developed hepatitis with jaundice and from whom two or more specimens were available; 6 of these individuals showed four-fold or greater antibody changes over a period of 3 to 6 months implying an etiological relationship between these cases and A-1 virus.

Antimicrobial Agents in Foodstuffs. Preliminary characterization of these substances has been completed. Five different antiviral and antibacterial paolins have so far been isolated from abalone, oyster and other shellfish. The first three are probably complex proteins, the fourth is most likely a histone and the fifth - a complex lipid. Their possible usefulness as an antimicrobial means of treatment and prevention of certain infections in experimental animals is being evaluated. In collaboration with the Laboratory of Infectious Diseases, NIAID, a study is underway to determine whether commercial clam juice fed daily to a nursery population will affect the incidence of bacterial and viral upper respiratory infections.

Avian Leukosis Viruses in Relation to Human Vaccines. The Rubin RIF test has been in use at DBS for detecting the avian leukosis viruses in the vaccines of chick embryo origin. Because the procedure is cumbersome and time consuming, several other techniques have been explored so far without success. It is planned to evaluate next the COFAL procedure, developed at NIAID, as a supplement or as an eventual replacement for the RIF test.

Arboviruses. Vaccines against certain arboviruses of public health importance may soon come within the purview of the Division. A small laboratory has been now established at DBS to provide the technical competency in arbovirus animal work, tissue culture and serology, to establish a reference collection of arthropod-borne viruses for the immediate and future needs of the Division and to utilize these resources in research on selected arboviruses, including those of importance as vaccine candidates.

Preparation of Cell Cultures for Research and Vaccine Test Use. A total of 468,980 tubes, 155,723 oz. bottles, 6,261 milk dilution bottles and 4,066 32 oz. bottles of standard and experimental primary and serial cell cultures for research and testing of viral vaccines were prepared during this period. These cultures provide an indispensable tool for the fulfillment of the vaccine testing responsibility of the Division and for the use by research investigators in this and other laboratories of DBS and even certain other Institutes.

Safety Testing of Inactivated Virus Vaccines in Cell Culture. Upon determining the viral susceptibility of the several cell systems, the cultures were used for safety testing of the killed virus vaccines. During the calendar year 1963 samples of 11 lots of inactivated poliovirus vaccine, 8 lots of adenovirus vaccine and 16 lots of measles vaccine were tested. This project fulfills a statutory responsibility of the Division.

PATHOLOGY UNIT

The Pathology Unit has continued its work with testing of Poliovirus, Vaccines, Live, Oral. The greatest bulk of the testing has been of the Type 3 vaccines since this is the type about which there had been some concern. The need for monitoring this vaccine type has been apparent and the neurovirulence has been evaluated very carefully. In conjunction with Dr. Clifford Maloney, O.D., statistical analysis of neurovirulence data has been performed and certain acceptance levels for neurovirulence have been adopted.

Investigations are continuing in the study of the relationship of neurovirulence and *in vitro* characteristics of attenuated polioviruses.

Studies are also continuing in the field of viral oncogenesis and efforts are underway to alter animal susceptibility to tumor viruses.

The Pathology Unit has expanded its collaborative studies to include almost all the other laboratories of the Division and has had an increasing number of animal tissues to process and thus has had to increase its technical personnel by two. The unit foresees increasing responsibilities and collaborative efforts with other groups at DBS.

Serial No. DBS 2
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Experimental Virology

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2 3/4
Professional: 1
Other: 1 3/4

Patient Days: None

Project Description:

The overall aim of this project is to investigate the safety of biological products, to study viruses that may serve as models for improving existing vaccines, to investigate new viruses for the purpose of exploring the possibility of preventing diseases that at present are uncontrolled and to fulfill the obligation of controlling anti-pneumococcus sera. Due to space and personnel limitations, of necessity only a limited number of viruses could be used. The viruses used were: the papova viruses, adenoviruses and miscellaneous or unclassified viruses.

Part B included Yes / / No /X/

1

Serial No. DBS 3
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Experimental Virology (Papova viruses)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1 5/12
Professional: 2/3
Other: 3/4

Patient Days: None

Project Description:

Work on one member of this group of viruses was started several years ago in an effort to gain information on the etiology of lung cancer and as a sideline in investigations of the known respiratory viruses. The original objective was to find a way to isolate a virus or viruses from human neoplasms and to find a way to prevent neoplasms in man. This is still an objective but it has been shelved for the present because of the importance of one of the papova viruses, simian virus 40 which is a contaminant of rhesus monkey kidney cell cultures used in production of certain virus vaccines. An understanding of the properties of the papova viruses may aid in investigations of other oncogenic or latent viruses. The immediate aim of the project will be to continue to study the properties of this group of viruses for the purpose of 1) determining the most effective way to detect and eliminate simian virus 40 and 2) to gain information that might be useful in investigations of human cancer viruses.

The activities include:

(a) Determination of the effect of certain physical and chemical agents, route of injection, dosage, age, and animal passage on induction of neoplasms in hamsters by simian virus 40. Along this line, hamsters infected with an oncogenic dose of simian virus when newborn could be prevented from developing neoplasms by the injection of repeated large doses of the same viable homologous virus starting some 15 to 60 days following the initial infecting virus dose. This is apparently an immunological phenomenon and work on it is being continued.

(b) Continuation of a collaborative study with Dr. Roger Weil, Universite de Geneve, Institut de Biologie Moleculaire, on the nucleic acid of purified simian virus 40. Dr. Weil moved from the California Institute of Technology to Geneva, so progress on this problem has been delayed.

(c) With Dr. Karl Habel in the National Institute of Allergy and Infectious Diseases, completed a study on an immunological comparison of simian virus 40 and polyoma virus induced neoplasms.

(d) Cell cultures from animals other than monkeys were infected with simian virus 40 and the cultures are being observed for morphological changes and for oncogenic activity in hamsters.

Work with the papova viruses is being continued in an effort to obtain information that may be useful for the overall project.

Part B included Yes / / No /X/

3

Serial No. DBS 4

1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Experimental Virology (Adenovirus)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2/3
Professional: 1/6
Other: 1/2

Patient Days: None

Project Description:

The objective of work with this group of viruses is to improve methods for evaluating the purity and safety of adenovirus vaccines and of assessing the oncogenic capacities of some of the types of adenoviruses.

The activities include:

(a) Oncogenic capacity of adenoviruses. The oncogenic properties of adenovirus types 12 and 18 are being studied. Like simian virus 40, neonatally infected hamsters infected with an oncogenic dose of adenovirus type 12 when newborn, could be prevented from developing neoplasms by the injection of repeated large doses of homologous type 12 adenovirus approximately 15 days after the initial infecting virus had been given. Work on this phenomenon is being continued.

(b) Work on other types of adenoviruses is being carried out in order to obtain more information concerning their relationship to development of neoplasms. As a prerequisite, new strains were isolated from throat washings in primary human cells in order to avoid contamination with simian viruses or contaminating agents which might be present in continuous line cells.

Certain phases of this work are being carried out in collaboration with Dr. Ariel Hollingshead at George Washington University.

Part B included Yes / / No /X/

Serial No. DBS 5
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Experimental Virology (Miscellaneous viruses)

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: One phase--Laboratory of Biophysics & Biochemistry, DBS

Man Years:
Total: 2/3
Professional: 1/6
Other: 1/2

Project Description:

The aim of this part of the project is to study new or little understood viruses, their hosts and pathogenic potentialities in order to obtain information necessary for investigating diseases of unknown etiology.

The activities include:

Different viruses have been studied from time to time. Because of the nature of the viruses and lack of space for proper isolation facilities, progress has been slow. Dr. C. W. Hiatt and Mr. John Theil are cooperating in a study of the morphological characteristics of these viruses.

Part B included Yes / / No /X/

5

Serial No. DBS 6
1. Experimental Virology
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Pneumococci

Principal Investigator: Dr. Bernice E. Eddy

Other Investigators: None

Cooperating Units: None

Man Years:
Total:
Professional: Insignificant

Project Description:

The objective of the project is to control pneumococcus typing sera. This is a minor project; only seven lots of pneumococcus typing serum mixtures were released in 1963.

The activities include:

Each lot was tested for potency for one or more of the component homologous types.

The major aim of the project is to fulfill the obligation of controlling pneumococcus typing sera.

Part B included Yes /X/ No /__/

6

Part B.

Publications:

1. Habel, K. and Eddy, B. E. Specificity of resistance to tumor challenge of polyoma and SV40 virus immune hamsters. Proc. Soc. Exp. Biol. and Med. 113 (1):1-4, May, 1963.

2. Eddy, B. E. Comparison of properties of two viruses -- SV40 and polyoma-oncogenic for hamsters. Perspectives in Virology, Hoeber Medical Division of Harper and Row, 3:138-158, 1963.

3. Eddy, B. E. Propiedades biologicas y patológicas del virus del mono "40." Acta Oncologica 2 (1):26-37, enero-junio, 1963.

Presentation of papers:

March, 1963. Seminar at Roswell Park, Buffalo, New York.
July, 1963. Lecture at Roswell Park, Buffalo, New York.
November, 1963. Paper presented to a joint meeting of the Laboratory and Epidemiology Sections and the Conference of Public Health Veterinarians, Am. Pub. Health Assoc., Kansas City, Missouri.

7

LABORATORY OF BACTERIAL PRODUCTS

Summary of Projects, January 1, 1963 through June 30, 1964

During the past 18 months while continuing the projects of the previous year, the Laboratory of Bacterial Products has placed special emphasis on the relation of laboratory evaluated potency to efficacy in man and has actively participated in three conferences on subjects directly related to the programs of the LBP.

Correlation of Laboratory Evaluated Potency of U.S. Reference Preparations with Human Response. Some years ago it was shown that mouse protective potency of pertussis vaccine was directly correlated with protection of children against whooping cough. The potencies of the field trial vaccines (British) were related to the U.S. Standard Pertussis Vaccine and the latter became the basis of reference for the establishment of the potency of the international standard. By request LBP is selecting a replacement for the first international standard pertussis vaccine. Potency again will be established in relation to the Master U.S. Standard.

Recently, in the laboratory evaluation of two typhoid vaccines, which in WHO sponsored field trials were found to afford significant protection, the U.S. reference typhoid vaccine was found to be inferior to either the acetone-killed-dried (AKD) or the heat-killed phenolized vaccine. Since the former was superior, an AKD vaccine has been procured by the Section on Reference Standards, LCA. The Section on Bacterial Vaccines is collaborating in the evaluation of the new preparation in relation to the field trial AKD vaccine.

The collaborative study on tetanus antitoxin response of pregnant women in Territory of Papua and New Guinea is providing valuable information relative to the laboratory evaluation of potency of tetanus toxoids. The laboratory potency of certain of the field trial toxoids are being compared with the international reference tetanus toxoid, plain, and the proposed international tetanus toxoid, adsorbed, as well as with the U.S. reference preparations.

Although in use many years, cholera vaccine has not been shown in controlled field trials to be efficacious in protecting man against cholera. Currently a trial is being carried out by the Pakistan-Cholera Research Laboratory, Dacca. Laboratory potency of the field trial vaccine has been related to the proposed U.S. reference vaccine by means of a revised potency test (SBV).

Studies on the relation of laboratory potency of vaccines to efficacy in man have been recognized by a Superior Service Award to the Chief of the Laboratory.

U.S. Standards of potency for allergens have not been developed.

Emphasis is being placed on development of a standard for poison ivy extract by the Section on Allergens. About 80% of the people in the U.S. are sensitive to poison ivy and contact dermatitis is a significant occupational hazard. Catechol content as determined by gas chromatography and guinea pig skin reactivity were found to be directly correlated. However, when tested on man, it was found that pentadecylcatechol was only one-tenth as active as the extract on certain subjects. Further work has been initiated to relate synthesized catechols to human skin reactivity and also to determine if indeed man can be desensitized with poison ivy extract.

Conferences. (1) The Section on Bacterial Vaccines organized a symposium on pertussis vaccine which was sponsored by the DBS and held at the NIH in October to discuss problems relating to the manufacture and control of the vaccine and untoward reactivity in children. An outgrowth of the meeting will be an investigation to relate pertussis vaccine reactivity in children to laboratory measured toxicity.

Two staff members, respectively, participated in two Round Table Conferences of the International Association of Microbiological Societies, Permanent Section of Microbiological Standardization, London, England. (2) At the Conference on Sterility Testing, Dr. Pittman presented a general paper on culture media and temperatures of incubation and another paper in which were given the results of the current sterility testing study by Mrs. Cox, Section on Bacterial Vaccines. Much progress was made in coming to an international agreement on the use of one medium and one temperature of incubation for the general sterility test and the use of additional procedures for specific products. (3) At the Round Table Conference on Tuberculin, Dr. Baer, Section on Allergenic Products, presented the recent new and significant finding by him and Dr. Chaparas that a carbohydrate fraction of tuberculin can induce delayed skin reactions.

Tuberculin. In their comprehensive studies on the characterization of fractions of tuberculin, Doctors Chaparas and Baer, SAP, in addition to the finding mentioned above, have shown that skin reactivity is associated with dialyzable and nondialyzable components and that the substances with greatest immunological activity dialyzed slowest and had the greatest sedimentation constants.

Poison Ivy Extract. Doctors Bowser and Baer, SAP, in their studies directed toward a U.S. Standard of potency of this extract found when guinea pigs were injected or fed pentadecylcatechol in vegetable oil that immunological unresponsiveness was induced. However, when the same solutions were mixed with mycobacteria and injected or applied to the skin, skin sensitivity was induced.

Rhesus monkeys failed to develop contact dermatitis to poison ivy.

Tetanus Toxoid. In the collaborative study of the Section on Bacterial Toxins on the prevention of neonatal tetanus in the Territory of Papua and New Guinea, it has been shown that the mean antitoxin response to one injection of toxoids in oil was significantly greater than the response to two injections of $AlPO_4$ adsorbed toxoid, and the latter was significantly

better than the response to three injections of plain toxoid. There is promise that in those countries where the rate of neonatal tetanus is high, women of child-bearing age could be successfully vaccinated with one injection of tetanus toxoid in oil.

Dr. Hardegree, SBT, in her study on the separation of antigenic components of cultural filtrates of Clostridium tetani has obtained partial separation of neurotoxin and hemolysin.

Pleuropneumonia-like Organisms. Dr. Barile, SBT, in collaboration with Dr. Shimke (NIAMD) has described a rapid chemical method for the detection of PPLO contamination in tissue cell cultures in which arginine is converted to ornithine by arginine deiminase which is present in the contaminated cultures but absent in noncontaminated cultures. The test is proving to be very helpful in the screening of tissue cultures for contamination. In his collaboratory work with Dr. Graykowski (NIDR) pure cultures of a transitional L-form were isolated repeatedly from lesions in recurrent aphthae patients.

Pertussis Vaccine. Mrs. Gardner, Section on Bacterial Vaccines, has shown that the preservative benzethonium chloride which was used in the quadruple antigen product in place of Merthiolate to prevent deleterious effect of mercury on potency of poliomyelitis vaccine, was the principal cause of loss of potency of pertussis vaccine in the combined product. A mixture of methyl- and propyl-p-hydroxybenzoate, a commonly used preservative in pharmaceutical products was found to be also harmful to pertussis vaccine. In the presence of tissue culture, with or without polio virus there was slight, but not significant, decrease in potency of pertussis vaccine with time.

Since the revision in the toxicity test for pertussis vaccine two and a half years ago, there has been an overall decrease in the mouse toxicity of the lots of pertussis vaccine submitted for release. Graded dose-response curves prepared by Mrs. Cox, SBV, show that the lots would meet the requirement at a higher dose level than specified. An analysis of the toxicity tests performed by SBV over a 9.5 year period showed a remarkable consistency with a trend towards decreased toxicity.

Typhoid Vaccine. Additional experiments have confirmed the findings of 1962, that by the intraperitoneal route and not by the subcutaneous route of vaccination can the difference in human protective response be measured in a mouse assay. The manufacturers of typhoid vaccine have been notified of the superiority of AKD vaccine. A reference AKD vaccine has been procured by Sections Reference Standards, LCA, and SBV is collaborating in its potency evaluation in terms of the field trial AKD vaccine.

Cholera Vaccine and Cholera Vibrios. The maximum dose of a cholera vaccine that does not cause a delayed reaction in man has been related to mouse toxicity and nitrogen content. These observations formed the basis for a revision in the bacterial content requirements for cholera vaccine. Other information obtained on cholera vaccine should permit the issuing of a complete revision of the requirements for cholera vaccine in the near future.

The recent spread of cholera to many countries in the Far East by vibrios that have some characteristics different from those that are the cause of endemic cholera in the Bengal area has stimulated much interest in the taxonomic characteristic of the cholera vibrios, their relation to epidemiology and efficacy of cholera vaccine. Dr. Feeley, SBV, is studying the characteristics of these epidemic strains and also the characteristics of non-cholera vibrios that are the cause of or are closely associated with an acute gastroenteritis.

Doctors Feeley and McIntyre, SBP, using the infant rabbit model to observe passive protection against experimental cholera have found that differences in protective activity are not necessarily reflected by in vitro measured antibody titers. Recently, Dr. Feeley has observed that protection is better with the lower molecular weight antibody than with the larger molecular weight antibody. The studies hold promise of a better understanding of the immune response to cholera vaccine and indirectly to the control of the quality of cholera vaccine.

Dr. J. Spaun, Visiting Scientist, is studying the factors of the cholera vibrio which affect the sodium permeability of the frog skin. The massive diarrhea of cholera is apparently due to disturbance of the sodium pump of the gut.

The Chief, LBP, is serving on the NIH Cholera Advisory Committee, the Pakistan-SEATO Cholera Research Laboratory Technical Advisory Committee, and as NIH Project Officer for the CRL.

Non-research Activities. During the period of January 1 to December 31, 1963, 597 tests were performed. These were for the control of pertussis vaccine, anti-pertussis serum and Haemophilus influenzae therapeutic and diagnostic sera.

Other regulatory activities consist of (1) submission of a proposed final draft of Additional Standards: Pertussis Vaccine for Proposed Rule Making Publication, and (2) participation in the review of license applications to determine eligibility of establishments and of individual products for license, inspection of establishments and liaison activities between the Division and one manufacturer of poliomyelitis vaccine.

Serial No. DBS 7
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Pertussis Vaccine

Principal Investigator: Dr. Margaret Pittman

Other Investigators: Mrs. Claire B. Cox
Mr. James F. Marshall

Cooperating Unit: None

Man Years:

Total:	3.5
Professional:	1.0
Other:	2.5

Project Description:

Objectives: The objective is that all lots of products containing pertussis vaccine issued by U. S. licensed establishments have optimum properties: adequate and stable potency throughout the dating period and relative freedom from untoward reactive substances.

Methods Employed: Mouse potency tests to determine adequacy of potency and stability of potency. Dose-response toxicity tests. Analyses of results of all toxicity tests performed since 1953.

Major Findings: The slopes of toxicity dose-response curves of plain, and Alum, $AlPO_4$ and $Al(OH)_3$ adsorbed pertussis vaccine were not significantly different.

The analyses of toxicity tests for a 9 year period show that there has been an overall downward trend in mouse toxicity of the vaccines.

Significance to bio-medical research and the program of the Division: The surveillance of and research on pertussis vaccine provides information relating to control and improvement of the product and basic scientific information about immunological and reactive properties of Bordetella pertussis.

Proposed Course of Project: Emphasis will be placed on investigating the relation of laboratory measured toxicity of pertussis vaccine to its reactivity in children.

Part B included Yes /X/ No / /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards and Publications

Margaret Pittman, Ph.D.

1963 Superior Service Award conferred by Department of Health, Education and Welfare

1962 Diplomate of the American Board of Microbiology granted by the American Academy of Microbiology.

Serial No. DBS 8
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Influence of preservatives and other factors on the instability of potency of pertussis vaccine

Principal Investigator: Mrs. Roberta A. Gardner

Other Investigators: Dr. Margaret Pittman

Cooperating Units: None

Man Years:

Total:	2.1
Professional:	1.5
Other:	0.6

Project Description:

Objectives: The primary objective was to determine the cause of the instability of pertussis vaccine in the presence of poliomyelitis vaccine.

Methods Employed: (1) The instability of pertussis vaccine in the presence of poliomyelitis vaccine was investigated by observing the effect of preservatives and various components of poliomyelitis vaccine on the potency of pertussis vaccine. (2) Attempts were made to find a rapid assay for pertussis vaccine.

Major Findings: (1) The use of benzethonium chloride as a preservative, rather than merthiolate, was an important reason for the instability of pertussis vaccine in the presence of poliomyelitis vaccine. Pertussis vaccines preserved with merthiolate were found to be more stable than vaccines preserved with benzethonium chloride. A combination of methyl- and propyl-p-hydroxybenzoate also was tried since they are used as preservatives in biologicals, but they also had a harmful effect upon pertussis vaccine potency. (2) The poliomyelitis virus did not appear to be a cause of the instability of the pertussis vaccine. (3) Tissue culture fluids with and without virus caused a slight but insignificant decrease in potency whereas with heated tissue culture fluids the decrease was even less. The possible role of enzymes or

other substances from the tissue culture fluid in causing instability of the pertussis vaccine appeared to be less important than the preservative. (4) A histamine-sensitization test appeared useful as a relatively rapid screening test for determining whether pertussis vaccines are potent. (5) Attempts to correlate chemical assays with pertussis vaccine potency were not successful.

Significance to Bio-medical Research and the Program of the Division: Research on pertussis vaccine provides information relating to improvement of the product, and also provides basic scientific information about the properties of Bordetella pertussis.

Proposed Course of Project: Investigation of the instability of potency of pertussis vaccine in the presence of poliomyelitis vaccine will receive less attention during the coming year. Further attempts to find rapid assay methods for pertussis vaccine will be made.

Part B included Yes /__/ No /X/

Serial No. DBS 9
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Investigations Concerning Sterility Testing

Principal Investigator: Mrs. Claire B. Cox

Other Investigators: Dr. John C. Feeley, Dr. Margaret Pittman, and Mr. James F. Marshall

Cooperating Units: None

Man Years:

Total:	0.67
Professional:	0.52
Other:	0.15

Project Description:

Objectives: The objectives of this study are to re-evaluate the procedures specified for the sterility test with a view to improving the test, not only by providing optimum conditions for the detection of the presence of contaminating bacteria, fungi and yeast, but also, by simplifying the procedures.

Methods Employed: The methods employed are those usually associated with sterility testing and experiments designed to observe the influence of temperature of incubation on the action of preservatives, length of incubation time, media and the inter-relation of these factors on the detection of fungi and yeasts in the presence of biologics (typhoid vaccine and 1.0% plasma).

Major Findings: Length of Incubation Time. Evidence obtained continues to support the previous findings that for maximum recovery of fungi in the presence of extremely low concentrations (3.0 - 5.0 parts/million) of mercurial preservatives 21 days of incubation are required. In the presence of dilute concentrations of benzethonium chloride, phenol or mixtures of methyl- and propyl paraben, detection of viability was obtained within 7 to 10 days.

Media: The results to date indicate that when mercurial compounds are used, the medium employed for maximum detection of fungi should contain some mercurial neutralizing substance. The media which

appeared to be most effective were Sabouraud Medium plus 0.5 gms/liter sodium hydrosulfite, Fluid Thioglycollate Medium, and Fluid Sabouraud Medium plus 0.5 gms/liter of sodium thioglycollate. Fluid Sabouraud Medium and Base Thioglycollate Medium plus 0.5 gms/liter sodium hydrosulfite were ineffective. Bonnel-Raby Sodium Hydrosulfite Medium was only moderately effective in neutralizing mercurials. In the absence of mercurials, the order of preference of media for growth of fungi was Bonnel-Raby, Sabouraud, Sabouraud plus thioglycollate, Sabouraud plus sodium hydrosulfite. In the presence of low concentrations of phenol, benzethonium chloride and a mixture of methyl- and propyl paraben, the order of preference was the same as in the absence of mercurials.

Preservatives: Merthiolate in concentrations of 1/10,000, 1/20,000 and 1/40,000 under simulated manufacturing conditions was fungicidal. Phenol in concentrations of 1:200, 1:250 and 1:400 had moderate fungicidal activity. Studies are underway to determine the effectiveness as fungicidal agents at 4°C of benzethonium chloride, phenylmercuric borate and a mixture of methyl paraben and propyl paraben.

Significance to Bio-medical Research and the Program of the Division: This project is of particular significance to the Division in relation to control of the safety and purity of biological products. Since it is essential that products be free of contaminating microorganisms throughout manufacture, the aim of the present study is to provide more sensitive methods for the detection of fungi and yeasts and at the same time try to simplify the testing procedure.

Proposed Course of Project: Further studies on the antimicrobial activity of other preservatives will be continued as well as a continuation of the media study.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards and Publications

M. Pittman participated in the Round Table Conference on Sterility Testing November 18--20, 1963, London, England and presented a paper entitled "Culture media and temperatures of incubation for the sterility test."

Serial No. DBS 10
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on Cholera Vaccine

Principal Investigator: Dr. John C. Feeley

Other Investigator: Dr. Margaret Pittman

Cooperating Units: NIH Cholera Advisory Committee

Man Years:

Total:	0.9
Professional:	0.45
Other:	0.45

Project Description:

Objectives: The establishment of an improved U.S. Standard of Potency and formulation of other requirements pertinent to the manufacture of this product.

Methods Employed: 1. The previously described mouse protection test has been used to evaluate the potency of additional lots of cholera vaccine produced by U. S. licensed and foreign establishments.

2. A study has been made of methods of controlling the antigen content of cholera vaccine. A relationship between opacity determinations, microscopic and colonial unit counts, and nitrogen content has been established. Studies have also been conducted to ascertain the feasibility of determining antigen content by a biological toxicity assay utilizing the weight loss induced in mice following injection of this endotoxic material.

Major Findings: Additional mouse protective assays of U.S. licensed cholera vaccines indicate that differences in potency between manufacturers continue to exist. Relative potency values for a given manufacturer indicate consistency in production. Vaccines from foreign establishments show even wider variations; some have potency comparable to U.S. products and others are much lower.

Data available at the present time indicate that an improvement in standardization of the antigen content of cholera vaccine may be achieved by the use of the opacity standard currently employed with Pertussis Vaccine, provided that suitable precautions to prevent lysis of the organism are observed. The opacity standards recommended by Minimum Requirements dated July 2, 1945 are technically difficult to employ and may result in incorporation of excess antigen in the vaccine. Chemical analysis for nitrogen content also proves valuable especially if performed on dialyzed samples or on material precipitable by 1.5 volumes of acetone. Determinations on dialyzed or acetone-precipitated samples reflect antigen content more accurately since they measure nitrogen associated with macromolecular cellular materials. Even total nitrogen determinations may be valuable for use with a standardized production procedure employing solid growth media; however, this method would not be applicable in those instances in which the organisms are grown in a broth medium which is incorporated directly in the vaccine.

Weight changes in mice may also be a valuable biological assay to detect excess antigen content. Weight loss on a dose-response basis correlates well with antigen content of vaccines as estimated by chemical methods and mouse protective activity. Clinical data on two lots indicate a direct correlation between mouse toxicity and untoward reactions in man.

Significance to Bio-medical Research and the Program of the Division: Although a considerable amount of information is now available on the antigenic potency of various cholera vaccines as measured by the mouse protection test, there is no information available to relate this activity with prophylactic efficacy, if any, in man. This information, of necessity, must await the execution of controlled field trials such as those contemplated by the WHO and the Pakistan-SEATO Cholera Research Laboratory (CRL).

Improved control over the antigen content of cholera vaccines must be exercised if untoward reactions are to be prevented. Clinical data, in conjunction with laboratory data on potency and antigen content have been valuable in suggesting an upper limit on the maximum antigenic dose tolerated by man. These findings have formed the basis for issuance of an amendment to Minimum Requirements: Cholera Vaccine, which specifies that the Opacity Standard for Pertussis Vaccine be employed under rigidly controlled conditions.

Proposed Course of Project: To carry through as indicated above. A manuscript describing the mouse protection test will be submitted for publication, and Additional Standards: Cholera Vaccine are being prepared for inclusion in Regulations.

Part B included Yes /X/ No / /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project.

Pittman, M. and Feeley, J. C. "Protective Activity of Cholera Vaccines Against El Tor Cholera Vibrios." Bull. Wld. Hlth. Org. 28: 379--383, 1963. (Listed in 1962 Report as in press.)

Serial No. DBS 11
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Immunologic Studies on Cholera in the Infant Rabbit

Principal Investigators: Dr. John C. Feeley
Dr. O. Ross McIntyre

Other Investigator: Mr. Andrew Young, LBB

Cooperating Units: Laboratory of Biophysics and Biochemistry

Man Years:

Total:	1.6
Professional:	1.0
Other:	0.6

Project Description:

Objectives: To investigate the activity of cholera immune sera in passive protection of the infant rabbit.

Methods Employed: Initially, an investigation was made of the ability of rabbit anti-cholera sera administered intraperitoneally 24 hours prior to challenge to protect 10--15 day old infant rabbits against intra-intestinal infection (Dutta's method) with Vibrio cholerae. Adult rabbits used for antiserum production were bled at intervals during the course of immunization and serum pools representing the various bleedings were prepared. In later studies conducted since Dr. McIntyre's departure, infant rabbits passively immunized with these sera were challenged orally by stomach tube, the inoculum being instilled following administration of a sodium carbonate solution. A larger inoculum was required to produce cholera regularly by this method.

Major Findings: Using the intraintestinal challenge method, complete protection was achieved in only 15% of animals, while in the remainder protection was evidenced only by a delay in onset of illness. All unprotected control animals died of the disease. It was not possible to demonstrate significant differences in protective activity of the various serum pools employed. Fatal infections were produced even if the vibrios were injected while suspended in high concentrations of antibody.

Using the oral challenge technique, it was shown that serum drawn early in immunization had only slight protective activity while

sera drawn later in the course of immunization were more protective. Thus, an increase in passive protective activity took place on prolonged immunization. Paradoxically, in vitro antibody titers did not correlate with passive protective activity in infant rabbits. Recent studies, using sucrose density gradient ultracentrifugation have shown that the early serum with low protective activity contains predominantly macroglobulin antibody, while sera with higher protective activity had predominantly lower molecular weight antibody.

Significance to Bio-medical Research and the Program of the Division: Unlike other laboratory animals, the infant rabbit develops a disease remarkably similar to human cholera and thus presents itself as an interesting model for immunologic studies. Unfortunately the young age at which the animal must be employed in relation to decreasing susceptibility to infection mitigates against satisfactory active immunization experiments. Nevertheless, passive immunization experiments may provide valuable information in relation to the mechanisms of protection against this infection. It is clear from the studies to date that differences in protective activity are not necessarily reflected by in vitro determined antibody titers. Since macroglobulin antibodies do not readily cross tissue membranes (e.g. placenta) it is quite feasible that such sera are not protective in the rabbit because they do not diffuse into the gut as coproantibody. However, further clarification of the role of coproantibody is indicated.

Future Course of the Project: Further studies are in progress to evaluate the role of size of antibody molecule in protection using gel filtration methods to obtain separation of antibodies of high and low molecular weight. Work completed to date is currently being prepared for publication.

Part B included Yes / / No /X/

Serial No. DBS 12
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Comparative Studies of Recently Isolated Cholera Vibrios

Principal Investigator: Dr. John C. Feeley

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	0.5
Professional:	0.25
Other:	0.25

Project Description:

Objectives: The acquisition of better descriptive information regarding the properties of recent epidemic strains of Vibrio cholerae to establish a more rational taxonomic and nomenclatural scheme for various biotypes.

Methods Employed: Routine bacteriological and serologic procedures supplemented by additional specialized tests for such properties as hemagglutination, hemolytic activity and sensitivity to bacteriophages are being employed. A comparison is being made of the properties of recent strains of V. cholerae from different geographic regions.

Major Findings: Although these studies are still in progress, it is apparent that cultures isolated during Western Pacific outbreaks in late 1962 and continuing through 1963 differ in certain characteristics from other strains involved in this geographic area in 1961--1962. Earlier strains, often called "El Tor vibrios," represented a biotype which was frankly hemolytic by both tube and plate hemolysis tests, hemagglutinated chicken cells, gave strongly positive Voges-Proskauer (VP) tests, and was phage resistant. This was quite distinct from the reactions of the "classic" biotype of V. cholerae which was nonhemolytic, nonhemagglutinating, weak or negative in the VP test, and phage sensitive. Recent isolates, on the other hand, seem somewhat transitional between the "classic" and "El Tor" biotypes, particularly with regard to

hemolytic activity. Some strains are frankly nonhemolytic, while others are weakly so or show a tendency toward development of mutants with widely differing hemolytic properties.

Significance to Bio-medical Research and the Program of the Division: Currently, much confusion exists concerning the taxonomy of vibrios capable of causing cholera in man. Some workers recognize a separate species, Vibrio el tor, which is differentiated from Vibrio cholerae (V. comma) on the basis of tests for hemolysis, hemagglutination and phage sensitivity. The present work indicates that these differences are subspecies in nature and that it is far more logical to recognize various biotypes of a single species, Vibrio cholerae. Recognition of a single species should help reduce the confusion which has prevailed among public health authorities as to the significance of the so-called "El Tor" vibrio. Further, a system for recognition of various biotypes should be of value, since some evidence already suggests that different biotypes may differ in their epidemiologic pattern.

Future Course of the Project: To carry through as indicated above to establish a subspecies biotype classification scheme.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project.

Feeley, J. C. and Pittman, M. "Studies on the hemolytic activity of El Tor vibrios." Bull. Wld. Hlth. Org., 28: 347-356, 1963. (Listed in 1962 Report as in press.)

Serial No. DBS 13
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Gastroenteritis Due to Noncholera Vibrios

Principal Investigator: Dr. O. Ross McIntyre

Other Investigator: Dr. John C. Feeley

Cooperating Units: Pakistan-SEATO Research Laboratory

Man Years:

Total:	0.50
Professional:	0.35
Other:	0.15

Project Description:

Objectives: To investigate the bacteriologic and serologic aspects of acute diarrheal disease apparently caused by noncholera vibrios (NCV's or NAG Vibrios).

Methods Employed: Paired sera and cultures from American and Pakistani subjects suffering from gastroenteritis in Pakistan are being investigated by routine serologic and bacteriologic methods in use in this laboratory. Cultures isolated are being characterized and paired sera from apparent cases have been examined for significant rises in antibody levels.

Major Findings: Noncholera vibrios (NCV's) are not infrequently isolated in Pakistan from stools of individuals with diarrheal disease. Symptoms vary from mild gastroenteritis to severe fulminating diarrhea resembling cholera. A total of 76 NCV cultures from 1700 cases of diarrhea of unknown etiology have been examined. In most cases, the NCV was the only abnormal organism isolated, and sometimes in nearly pure culture. Unfortunately, adequate histories and paired sera were available from only 13 cases. A significant rise in agglutinin titer against the NCV isolated from the patient occurred in 6 of the 13 cases.

Significance to Bio-medical Research and the Program of the Division: The present study, while by no means offering proof of an etiologic relationship, contains suggestive evidence that NCV's may cause or contribute to diarrheal disease in man. This seems particularly plausible in those cases from which the NCV was found in nearly pure culture as the only abnormal organism present and in which a significant rise in titer could be noted between acute and convalescent sera.

Several studies by others have shown that a significant proportion of cases of diarrheal disease do not yield any recognized pathogens on culture. Unfortunately, culture methods for pathogenic members of the family Enterobacteriaceae are largely unsuitable for isolation of cholera and noncholera vibrios. Even if isolated, it is very likely that bacteriologists who slavishly follow time honored methods for identification would promptly relegate them to the "paracolon" group due to their superficial resemblance to common enteric bacteria and their characteristic slow-lactose fermentation, a particularly sobering thought in the case of the cholera vibrio. In view of this situation and the reported ubiquity of vibrios in surface waters, it is felt that some consideration should be given to their possible etiologic role in diarrheal disease in areas other than Pakistan.

Future Course of the Project: Manuscripts describing the above information are in preparation. Publication has been delayed pending receipt of further data from Pakistan.

Part B: included Yes /__/ No /X/

Serial No. DBS 14
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on the Specificity of Tuberculin

Principal Investigators: Dr. Harold Baer
Dr. S. D. Chaparas

Other Investigators: Dr. C. W. Hiatt (LBB)
Mr. Andrew M. Young (LBB)

Cooperating Units: Laboratory of Biophysics & Biochemistry

Man Years:

Total:	1.3
Professional:	0.7
Other:	0.6

Project Description:

Objectives: To prepare tuberculins with greater specificities than those currently available.

Methods Employed: Culture filtrates and extracts of the BCG strain of Mycobacterium tuberculosis after having been separated into dialyzable and nondialyzable components are fractionated chemically, chromatographically on columns, and electrophoretically. Fractions thus prepared are tested for specificity of their tuberculin activity in guinea pigs sensitized with several species of mycobacteria.

Major Findings: Skin activity has been found to be associated with both the dialyzable and nondialyzable constituents. Of the non-dialyzable substances one fraction which is largely carbohydrate has been found to possess a degree of species specificity. Subfractionation attempts by means of electrophoresis have not been successful in further defining the specific skin reaction substances.

Significance to Biomedical Research and the Program of the Division: The isolation of highly specific tuberculins should result in more meaningful epidemiological surveys for tuberculosis and tuberculosis-like infections and in the preparation of reliable and reproducible standards.

Proposed Course of Project: Continue attempts toward the isolation of highly specific tuberculins.

Part B included Yes /X/ No //

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project.

Baer, Harold and Chaparas, S. D.: The Immunology and Chemistry of Tuberculin. I. The Isolation of Dialyzable and Nondialyzable Tuberculin-Active Components from Unheated BCG Culture Filtrates. Amer. Rev. Resp. Dis. 88 (1): 28, 1963.

Chaparas, S. D. and Baer, H.: The Immunology and Chemistry of Tuberculin. II. Chromatography with Sephadex of the Nondialyzable, Tuberculin Active Constituents of BCG Culture Filtrate, Amer. Rev. Resp.Dis. 89 (1): 41, 1964.

Serial No. DBS 15
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Properties of Dialyzable Tuberculins

Principal Investigators: Dr. Sotiros D. Chaparas (DBS)
Dr. Harold Baer

Other Investigators: Dr. C. W. Hiatt (LBB)
Mr. Andrew M. Young (LBB)

Cooperating Units: Laboratory of Biophysics & Biochemistry

Man Years:

Total:	1.3
Professional:	0.8
Other:	0.5

Project Description:

Objectives: To investigate the properties of the dialyzable constituents from BCG culture filtrates and ascertain whether these may be useful in skin-testing procedures.

Methods Employed: Concentrated dialysates separated by Sephadex chromatography into four groups. Their chemical, ultracentrifugal and dialysis properties were determined. The tuberculin activity in sensitized guinea pigs was assayed and antigenic analyses were done by gel precipitation reactions.

Major Findings: The immunologic activity as expressed by skin reactivity in sensitized guinea pigs and gel precipitin band formation was greatest with the first eluted substances and decreased in order of elution from the column. The greatest immunological activity was associated with substances which had the greatest sedimentation constants and dialyzed most slowly. Tuberculin active dialyzable materials have also been found in PPD-S and the Danish PPD-RT23.

Significance to Bio-medical Research and the Program of the Division: Small dialyzable components with skin reactivity because of their lesser complexities should be very useful in studies concerned with the chemical and immunological nature of tuberculin active compounds.

Proposed Course of Project: Further fractionations are planned. The skin reactivity of the new fractions shall be determined as well as the ability of the very small, almost inactive constituents to alter tuberculin reactions elicited by the larger nondialyzable and dialyzable constituents.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

S. D. Chaparas and H. Baer: The Immunology and Chemistry of Tuberculin. III. Dialyzable BCG Culture Filtrate Components Obtained by Sephadex Chromatography and Fractional Dialysis. Amer. Rev. Resp. Dis. Accepted for publication. (In Press).

Serial No. DBS 16
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Standardization of Poison Ivy Extracts

Principal Investigators: Dr. Harold Baer
Dr. Robert Bowser
Dr. Robert Auerbach (NCI)

Cooperating Unit: Dermatology Branch, National Cancer Institute

Man Years:

Total:	1.9
Professional:	0.9
Other:	1.0

Project Description:

Objectives: (1) Investigate the feasibility of producing a standard of potency for poison ivy extracts. (2) Study the immunology of poison ivy extracts and one of its components, 3-pentadecylcatechol (PDC).

Methods Employed: Further work is being done to relate the weight of total solids and catechols in extracts to the gas chromatographic and guinea pig assays. The gas chromatographic analyses are being done at the Applied Science Laboratories in Pennsylvania.

A program of skin testing humans was initiated. The purpose of this work is to relate human skin sensitivity to the guinea pig assay.

Immunologic unresponsiveness resulting from the injection and feeding of pentadecylcatechol has been studied as well as the effect of age of guinea pigs on their ability to become sensitized.

Major Findings: It was found that guinea pigs could be made sensitive even when they had reached their average life span (2-3 years), but that the degree of sensitivity induced was less with advancing age.

When guinea pigs are injected or fed with pentadecylcatechol in

vegetable oil solution, it becomes difficult or impossible to induce skin sensitivity. While these two routes of administration induce immunologic unresponsiveness, application of the same solutions to the skin or injection when emulsified with mycobacteria does induce skin sensitivity.

Skin test studies on humans indicated that pentadecylcatechol is about 1/10 as active as poison ivy extract. The data indicated that for humans there might be skin reactive components other than catechols.

Significance to Bio-medical Research and the Program of the Division: In this project attempts are being made to learn about the basic immunological phenomena associated with poison ivy sensitivity. It should be possible, eventually, to determine the composition and concentration of ingredients in extracts used for skin testing and desensitization.

Proposed Course of Project: Studies on basic immunology and chemistry of poison ivy extracts will continue along with further study and improvement of assay methods. Purified components of poison ivy extracts as well as synthetic substances related to the active principles are being prepared under contract. In this way a better understanding will be gained of the relationship of poison ivy sensitivity and the chemistry of the active components.

A contract is under consideration to enable a study to be made of desensitization of humans sensitive to poison ivy.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B: Honors, Awards, and Publications.

Publications other than abstracts from this project.

Baer, H. and Bowser, R. T. Antibody Production and Development of Contact Skin Sensitivity in Guinea Pigs of Various Ages. Science 140: 1211, June, 1963.

Bowser, R. T. and Baer, H. Contact Sensitivity and Immunologic Unresponsiveness in Adult Guinea Pigs to A Component of Poison Ivy Extract, 3-n-pentadecylcatechol. J. Immunol. 91: 791, December, 1963.

Serial No. DBS 17
1. Bacterial Products
2. Allergenic Products
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Toxicity and Sensitization Studies with Poison Ivy Extracts

Principal Investigators: Dr. Robert Bowser
Dr. Ruth Kirschstein (LVI)
Dr. Harold Baer

Other Investigators: None

Cooperating Unit: Laboratory of Viral Immunology

Man Years:

Total:	1.1
Professional:	0.3
Other:	0.8

Project Description:

Objectives: To determine whether feeding or injecting poison ivy extracts or pentadecylcatechol will induce pathological changes unrelated to sensitization.

Methods Employed: (1) Rhesus monkeys were given poison ivy extract and pentadecylcatechol, dissolved in vegetable oil, orally and parenterally over a 4-month period. Blood and serum analyses were performed before and during the study. The animals were then necropsied and tissues examined grossly and by stained microscopic section.

Since it would be preferable to study sensitized rather than normal animals attempts were made to sensitize the monkeys prior to treatment. Attempts to produce contact sensitivity in the Rhesus monkeys to poison ivy extract or pentadecylcatechol were unsuccessful.

(2) Pregnant guinea pigs were treated orally and parenterally with same preparations.

Major Findings: (1) No pathological changes were induced in the monkeys and the guinea pigs gave birth to normal litters. (2) Rhesus monkeys did not develop contact dermatitis to poison ivy.

Significance to Bio-medical Research and the Program of the Division: Poison ivy extracts have been employed for the desensitization of humans for many years with no apparent harmful effects. The present study, using monkeys, confirms this in a study in which the quantity of extract was determined by guinea pig assay. These results provide some assurance that the treatment of humans at the dosage levels employed should be a safe procedure.

Proposed Course of Project: The material is being prepared for publication; no further work is anticipated.

Part B included Yes /__/ No /X/

Serial No. DBS 18
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: The Schick Test Toxin (Diphtheria)

Principal Investigator: Dr. Michael F. Barile

Other Investigators: Mr. Donald B. Riggs
Mr. Robert W. Kolb (LCA)

Cooperating Unit: Laboratory of Control Activities, DBS

Man Years:

Total:	0.1
Professional:	0.1
Other:	0:0

Project Description:

Objectives: (1) To establish and standardize the potency, combining-power, and stability of the dried U.S. provisional Diphtheria Toxin Reference. (2) To develop a more accurate method for potency assay of Diphtheria Toxin for the Schick test. (3) To consider revision of specifications for Diphtheria Toxin for the Schick test.

Methods Employed: Potency was determined by skin reaction (MRD) and lethal response (MLD). Combining-power was established by the Lf and L+ determinations. Certain chemical and physical properties were also established.

Major Findings: Experimental work has been completed. Findings were given in an earlier report.

Significance to Bio-medical Research and the Program of the Division: The present study will provide background information for the re-evaluation of the present requirements and a revision of standards for Diphtheria Toxin for the Schick test.

Proposed Course of Project: The proposed potency assay and Standard Diphtheria Toxin for the Schick test have been submitted to manufacturers for comment. Preparation of findings for publication is being made.

Part B included Yes /__/ No /X/

Serial No. DBS 19
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Investigation of Tetanus Toxoids for Prevention of Neonatorum Tetanus

Principal Investigators: Dr. Margaret Pittman
Dr. Michael Barile
Dr. M. Carolyn Hardegree

Other Investigators: Dr. Edward B. Seligmann, Jr., LCA
Dr. Frank Schofield, New Guinea

Cooperating Units: Department of Public Health, Territory of Papua and New Guinea
Laboratory of Control Activities, DBS

Man Years for LBP:

Total:	4.7
Professional:	1.6
Other:	3.1

Project Description:

Objectives: Neonatorum tetanus is an important cause of infant mortality in a number of areas in the world. Prevention by means of vaccination of pregnant women is under investigation in New Guinea. The main objective of the LBP part of the project is to correlate laboratory assay of tetanus toxoids with field trial response and to relate the results to U.S. Reference tetanus toxoids (tested concurrently in animals) and the requirements for this product.

Methods Employed: (1) Potency assay of toxoids in guinea pigs by titration of antitoxin response by means of mouse neutralization and hemagglutination tests. (2) Antitoxin titrations of human sera by the mouse and hemagglutination tests to determine response of the women to different types of tetanus toxoid. (3) Statistical analyses of the laboratory results.

Major Findings: Antitoxin responses to two tetanus toxoids, each in a different oil and given in one dose were not significantly different. Likewise, there was no significant difference in the responses to two

plain toxoids given in 3 doses. However, the antitoxin titers of women injected with one dose of toxoids in oil were significantly higher than those injected with either 2 doses of toxoid, $AlPO_4$ adsorbed, or 3 doses of plain toxoids. The response to the $AlPO_4$ product was significantly higher than the responses to the plain toxoids.

Significance to Bio-medical Research and the Program of the Division: The demonstration that antitoxin response to one injection of tetanus toxoid containing an oil adjuvant is equal to or better than two injections of $AlPO_4$ adsorbed tetanus toxoid could facilitate the prevention of neonatal tetanus in developing countries.

Information obtained concerning the relative value of various quantitative methods of titrating tetanus toxoids and antitoxin will be applicable to the improvement of the present official tests.

Proposed Course of Project: (1) To prepare for publication the laboratory and clinical findings of the above described project, and (2) to determine the duration of antitoxin responses to oil and $AlPO_4$ adjuvant containing tetanus toxoids and the influence of a booster dose of either $AlPO_4$ adjuvant or plain toxoid given during pregnancy. All women of childbearing age of Territory of Papua and New Guinea are being vaccinated with either oil or $AlPO_4$ adjuvant containing tetanus toxoids.

Part B included Yes /__/ No /X/

Serial No. DBS 20
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: A study of the Antigenic Products of Various Strains of Clostridium tetani.

Principal Investigator: M. Carolyn Hardegree, M.D.

Other Investigators: None

Cooperating Units: None

Man Years:

Total:	1.0
Professional:	0.55
Other:	0.45

Project Description:

Objectives: (1) To determine the antigens present in culture filtrates of different strains of Cl. tetani. (2) To separate the antigens present in the filtrates, in particular, neurotoxin from hemolysin. (3) To study the relationship of these antigens to optimal anti-tetanus immunization.

Methods Employed: (1) Gel diffusion techniques. (2) Immuno-electrophoresis. (3) Zone electrophoresis. (4) Column chromatography. (5) Animal bioassay. (6) Animal immunization.

Major Findings: The Massachusetts C2 strain produces a potent neurotoxin and hemolysin, in addition to other unidentified proteins, when grown on a non-protein medium. Using electrophoresis and Sephadex gel filtration, a partial separation of these components has been achieved.

Significance to Bio-medical Research and the Program of the Division: Purified tetanal neurotoxoid may not provide optimal protection against tetanus. Other antigenic components of the organism may be important. It is necessary to know the identity of these antigens and to have them isolated before their role in immunization can be determined. The investigator believes these studies may help explain some of the questions that exist regarding antitoxin unitage titration, flocculation

zones, etc. These questions are relevant to the functions of the Division.

Proposed Course of the Project: Continued application of the methods above in the attempt to separate neurotoxin and hemolysin. Immunization of animals with the products obtained. Examination of the *in vivo* activity of the hemolysin in animals. Examination of the cardiotoxic activity of the two toxins. Attempts to identify other constituents will be made.

Part B included Yes / / No /X/

Serial No. DBS 21
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Standardization of Reference Preparations for Tetanus Toxoids

Principal Investigators: Dr. Margaret Pittman
Dr. Michael Barile
Dr. Carolyn Hardegree
Mr. Robert Kolb (LCA)
Dr. Edward B. Seligmann (LCA)

Cooperating Units: Laboratory of Control Activities, DBS
World Health Organization

Man Years for LBP:

Total:	0.5
Professional:	0.2
Other:	0.3

Project Description:

Objectives: By invitation the Division of Biologics Standards is collaborating in the standardization of the proposed international reference for tetanus toxoid, adsorbed. Additional objectives are to standardize the potency of the U.S. reference tetanus toxoids in relation to the international preparations, to correlate laboratory potency of tetanus toxoid to clinical response obtained in Territory of Papua and New Guinea and finally to improve the U.S. potency assay of tetanus toxoid.

Methods Employed: Graded dose protective response of the toxoids in assays using both mice and guinea pigs. Protective response is measured (1) by challenge with toxin, and (2) by mouse antitoxin titrations of the guinea pig sera obtained prior to challenge.

Major Findings: Not yet available.

Significance to Bio-medical Research and the Program of the Division: The international tetanus toxoid, adsorbed, will serve as a basis of reference whereby worldwide uniformly standardized tetanus

toxoid could be attained. The U.S. reference toxoids standardized in relation to the international preparation and correlated with clinical response will provide means for better standardization in U.S.

Proposed Course. To proceed as outlined above.

Part B included Yes /__/ No /X/

Serial No. DBS 22
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Pleuropneumonia-like Organisms

Principal Investigators: Dr. Michael F. Barile
Dr. Robert T. Schimke (NIAMD)
Dr. Joseph J. Bunim (NIAMD)
Dr. Alan S. Rabson (NCI)

Other Investigators: Mr. Donald Riggs
Mrs. Marian Grabowski

Cooperating Units: National Institutes of Arthritis and Metabolic Diseases
National Cancer Institute

Man Years:

Total:	0.6
Professional:	0.3
Other:	0.3

Project Description:

Objectives: (1) To develop new methods or to examine existing methods for detection of PPLO in cell cultures and biologic products, particularly, measles virus vaccine. (2) To develop methods for elimination of PPLO from cell cultures and biologic products. (3) To examine the role of PPLO in infectious diseases of man and animals.

Methods Employed: (1) The arginine deiminase assay procedure was developed as a new method of detecting PPLO in contaminated cell cultures. (2) Standard culture procedures were used for growth of PPLO.

Major Findings: (1) Arginine degradation is a significant metabolic process for PPLO isolated from cell culture and possibly a major source of adenosine triphosphate for this class of organisms. (2) Conversion of arginine to ornithine in PPLO-contaminated cell cultures occurred by the arginine dihydrolase pathway. (3) The presence of arginine deiminase in cell cultures contaminated with PPLO but absent in cell cultures free from PPLO was used as a rapid chemical method for

detection of PPLO. (4) No information is available on other studies.

Significance to Bio-medical Research and the Program of the Division: In view of the requirements for determining the presence of PPLO in viral products, these studies will provide information for establishing standards for these products. Arginine degradation by PPLO was exploited to develop a test for the presence of PPLO in cell cultures.

The 3-enzyme arginine deiminase pathway provides PPLO an economical means of obtaining adenosine triphosphate and presents a mechanism to explain why PPLO are the smallest free-living organisms.

Proposed Course of Project: To pursue studies to improve methods for the elimination and detection of PPLO in biological products.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Schimke, R. T. and Barile, M. F., Arginine Breakdown in Tissue Culture Contaminated with Pleuropneumonia-like Organisms (PPLO), Exptl. Cell Res. 30: 593-596, June, 1963.

Schimke, R. T. and Barile, M. F., Arginine Metabolism in Pleuropneumonia-like Organisms Isolated from Mammalian Cell Culture, J. Bacteriol. 86: 195--206, August, 1963.

Barile, M. F. and Schimke, R. T., A Rapid Chemical Method for Detecting PPLO Contamination of Tissue-Cell Cultures, Proc. Soc. Exper. Biol. & Med. 114: 676-679, December, 1963.

Serial No. DBS 23
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Recurrent Aphthae

Principal Investigators: Dr. Edward A. Graykowski NIDR
Dr. Michael F. Barile

Other Investigators: Dr. Edward Driscoll NIDR
Dr. Harold Stanley NIDR
Mr. Donald Riggs
Mrs. Marian Grabowski

Cooperating Units: National Institute of Dental Research

Man Years:

Total:	0.5
Professional:	0.2
Other:	0.3

Project Description:

Objectives : To examine the role of transitional L-forms in the pathogenesis of recurrent aphthae.

Methods Employed: (1) Recurrent aphthae lesions were examined by culture and histopathologic examination to establish the incidence of transitional L-forms in these lesions. (2) These organisms were inoculated in the skin and oral cavity of rabbits and guinea pigs to determine their virulence for animals.

Major Findings: (1) Pure cultures of a transitional L-form were isolated from numerous lesions in 7 recurrent aphthae patients, from blood during 2 exacerbations of one patient and from the biopsied scar-tissue of a previous lesion during quiescence. A prototype strain of the transitional L-form produced lesions in rabbit skin which showed all of the clinical characteristics of lesions seen in periadenitis aphthae. On histopathologic examination, the lesions produced in rabbits showed many of the characteristics of the cellular response seen in the lesions of patients.

Significance to Bio-medical Research and the Program of the Division: In view of requirements for absence of PPLO (and/or L-forms of bacteria) in viral products, these studies will provide information relative to the functions of the Division. These findings will be useful in establishing the etiology of recurrent aphthae and subsequently may provide a means by which the disease may be arrested, particularly, prevention by vaccination.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Barile, M. F. and Graykowski, E. A., Primary Herpes, Recurrent Labial Herpes, Recurrent Aphthae and Periadenitis Aphthae: A review with some new observations, Dist. Columbia Dent. J. 2: 7-15, July, 1963.

Barile, M. F., Graykowski, E. A., Driscoll, E. J., and Riggs, D. B., L-forms of Bacteria Isolated from Recurrent Aphthous Stomatitis Lesions, O.A., O.M. and O.P. 16: 1395--1402, November, 1963.

Serial No. DBS 24
1. Bacterial Products
2. Bacterial Toxins
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Bacterial Meningitis

Principal Investigator: Dr. Sara E. Branham

Other Investigators: None

Cooperating Units: None

Man Years:
Total: None
Professional: None
Other: None

Project Description:

This project was terminated in 1959. A publication for this project is given in Part B.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Branham, S. E.: Bacterial Meningitis. In Harris and Coleman (Eds.): Diagnostic Procedures and Reagents, New York City, American Public Health Association, Inc., 1963, 4th Ed., Chapter XVI, pp. 426-461.

Serial No. DBS 25
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Haemophilus Infections

Principal Investigator: Dr. Margaret Pittman

Other Investigators: None

Cooperating Units: None

Man Years:
Total: None
Professional: None
Other: None

Project Description:

This project was terminated in 1962. A publication for this project is given in Part B.

Part B included Yes /X/ No /___/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Pittman, M.: Hemophilus Infections. In Harris and Coleman (Eds.): Diagnostic Procedures and Reagents, New York City, American Public Health Association, Inc., 1963, 4th Ed., Chapter XV, pp. 414-425.

Serial No. DBS 26
1. Bacterial Products
2. Bacterial Vaccines
3. Bethesda, Md.

PHS-NIH
Individual Project Report
September 1, 1963 to June 30, 1964

Part A

Project Title: In vitro production of sodium pump inhibitors by Vibrio cholerae

Principal Investigator: Dr. Jorn Spaun, Visiting Scientist

Other Investigator: None

Cooperating Unit: International Laboratory for Biological Standards, Statens Seruminstitut, Copenhagen, Denmark

Man Years:

Total:	1.6
Professional:	0.8
Other:	0.8

Project Description:

Objectives: According to the present concept, the pathogenesis of cholera is an inhibition of the sodium transport in the intestine due to metabolic products of the cholera vibrio. Clinical as well as experimental indications in favor of this theory have been reported in recent years. The experimental evidence has chiefly been obtained by means of one commercially available crude filtrate of cholera culture, the potency of which has proved highly variable from batch to batch. After the experiments were confirmed and extended as to their possible immunological significance at the International Laboratory for Biological Standards, the first objective was to define the conditions for the successful reproducible production of sodium pump inhibitors in vitro.

Methods Employed: The test for presence of sodium pump inhibitors produced by in vitro cultures has been by means of the procedure for measuring active sodium transport of the isolated frog skin, as developed by Ussing in Copenhagen.

Major Findings: While the International Laboratory for Biological Standards, Copenhagen, has utilized traditional bacteriological media, the work here has been focused on cultivation of Vibrio cholerae in tissue cultures of different kinds under various conditions. So far, these studies have not proved successful. Recently, attention has also been concentrated on the metabolites developed in traditional culture media, but the results obtained are ambiguous.

Significance to Bio-medical Research and the Program of the Division: The possible specific immunological neutralization of the sodium pump inhibitors, as demonstrated previously, together with the demonstration of sodium pump inhibitors in some production batches of cholera vaccine suggests the possibility of a new bio-assay for cholera immunologicals. The assay method described is known to be an exact quantitative reflection of the sodium transport mechanism. Contrary to any other available laboratory potency assay, the specificity of this assay system is thus highly significant, and it is important to determine its usefulness in the laboratory control of cholera immunologicals.

Proposed Course of Project: This project will be continued at the International Laboratory for Biological Standards.

Part B included Yes / / No /X/

LABORATORY OF BIOPHYSICS AND BIOCHEMISTRY

A major undertaking during 1963 was the establishment of a unit within the Laboratory of Biophysics and Biochemistry to provide for a systematic program of chemical analysis of biological products. This group, which is under the supervision of Dr. Jerome J. Helprin, consists of four chemists and occupies three laboratory modules. The function of the group is to perform chemical and physical analyses of licensed biologicals, products under development, and materials of research, as well as to conduct research in the development of methods and in the correlation of chemical composition with biological properties.

The long-range research program of the laboratory, identified primarily with the application of physical principles to microbiological systems, has continued at a reduced pace because of the reassignment of space and loss of personnel. Dr. John M. Easton completed an intensive study of the multiplication of SV_{40} in rhesus kidney cells. Dr. Nobuto Yamamoto, whose appointment as visiting investigator terminated in October 1963, contributed some interesting information on bacteriophage genetics prior to leaving NIH to join the staff of the Fels Research Institute at Temple University. Miss Dorothy E. Moore, who had carried out many of the virological experiments, left her job to extend her graduate study at the University of Chicago. Reorganization of the research program of the laboratory to match the personnel and space now available will be an important responsibility in the forthcoming year.

Serial No. DBS 27
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Studies of the inactivation of viruses.

Principal Investigators: C. W. Hiatt, Ph.D., Nobuto Yamamoto, Ph.D., and Dorothy Moore, B.A.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 4.30
Professional: 1.60
Other: 2.70

Project Description:

Objectives: (1) To gain information about the fundamental nature of the various biological properties of viruses through studying the mechanisms of inactivation of these properties by physical and chemical agents.

(2) To develop an understanding of processes of inactivation that may be applied to the preparation of viral vaccines.

Methods Employed: Various animal and bacterial viruses are cultivated in cell cultures and the infective fluids from these subjected to treatment with graded doses of the inactivating agent. Samples taken at the different dosage levels are assayed for infectivity, and the kinetic relationship between dose and survival ratio is established. From the characteristics of the survival curve inferences are drawn about the properties of the virus and the mechanism of the inactivating process.

Major Findings: (1) Isolation of virus-free infective centers for poliovirus. Poliovirus propagated in the dark in cell cultures containing proflavine (2 mcg/ml) becomes sensitive to light and may be destroyed by subsequent exposure to visible light. By utilizing this phenomenon, we have been able to interrupt the process of infection of tissue-culture cells during the eclipse phase and to destroy virtually all of the cell-associated virus persisting from the inoculum. Some of the cells remain as potential infective centers although essentially no virus is left in the system. In a typical experiment, $LLMK_2$ cells in suspension are inoculated with photosensitive poliovirus at a multiplicity of 1. After 20 minutes incubation at 36° in the dark, the suspension is centrifuged, washed with buffer and resuspended. At this stage there are 10^5 viable cells/ml. After irradiation for 5 minutes at standard light flux, 10 to 100 infective centers/ml remain. If the suspension is subjected to 3 cycles of alternate freezing and thawing, however, and centrifuged to remove cell debris, no poliovirus is recovered in as much as 130 ml of fluid.

(2) Kinetics of photodynamic inactivation of coliphages. Photodynamic inactivation curves for f1, the male-specific rod-shaped coliphage described by Zinder, using toluidine blue as the photosensitizer, indicate a single-hit photochemical process preceded by a sensitizing reaction which is slow and temperature dependent. Such reactions have been regarded as signifying the existence of a functional membrane which restricts access of the dye to the nucleic acid core of the virus. At the present time it is not clear how this finding may be reconciled with the morphological simplicity of the phage.

(3) Action spectra for photodynamic inactivation of coliphages. Suspensions of T3 coliphage sensitized with toluidine blue were irradiated for graded time intervals with essentially monochromatic light from a grating monochromator. Velocity constants for the inactivation reaction were plotted as a function of wave length to a practical action spectrum which was almost identical with the visible absorption spectrum for toluidine blue. Similar experiments with f2 (RNA) coliphage suggest that the center of action spectrum is 500 A lower than the center of the absorption spectrum of the dye. The significance of this apparent metachromatic effect in terms of dye-binding is under investigation.

(4) Inactivation of bacteriophages by metals. We have observed that the RNA coliphages MS2 and f2 and, to a lesser extent, the single-stranded DNA phage S13 are inactivated when their dilute suspensions come into contact with an aluminum surface, or when they are diluted with fluids which have been in contact with aluminum, zinc, or magnesium. The inactivation has been shown to result from the simultaneous action of traces of Cu^{++} and electrolytically formed H_2O_2 and may be simulated by addition

of both of these agents, although neither alone is fully active when present in trace amounts. The phages are protected by adding either catalase or ethylene diamine tetraacetic acid (EDTA), which is further support for the suggested mechanism.

Significance to the Program of DBS. The continued investigation of the mode of action of viral inactivating processes is expected to contribute to the fundamental basis for control of viral vaccines.

Proposed Course of Project. This project will be continued.

Part B included Yes /__/ No /X_/

Serial No. DBS 28
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Physical characterization of biological substances.

Principal Investigator: Andrew M. Young, M.S.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1.5
Professional: 1.5
Other: 0

Project Description:

Objectives: To obtain information about the physical dimensions of biological substances and to correlate this information with biological properties.

Methods Employed: Standard methods of physical analysis, including ultracentrifugation, are supplemented by specialized techniques for fractionating and concentrating proteins and other macromolecular substances.

Major Findings: (1) Forty samples of human plasma and rat and mouse urine, which had been fractionated by gel filtration or DEAE chromatography by Dr. Finlayson of LBBP were analyzed in the ultracentrifuge so that the sedimentation constants of their normal protein constituents could be calculated, and the purity of the fractions could be determined. The sedimentation constants ranged from 2-10 x 10^{-13}.

(2) Outdated commercial preparations of albumin which had been stored at room temperature and above were analyzed in the ultracentrifuge to determine if there had been any deterioration of the proteins. When two such samples were compared with two in-date samples which had been stored at 2-10C no appreciable differences could be ascertained when the sedimentation constants were compared.

(3) One sample each of prothrombin and of thrombin which had been treated with diisopropylfluorophosphate were analyzed in the ultracentrifuge to determine if the treatment had changed the sedimentation constants when compared with untreated materials. It was found that the derivatives had smaller sedimentation constants than the untreated materials, and that conversion of prothrombin to forms intermediate to thrombin was inhibited by the diisoprophylfluorphosphate.

(4) Twenty-five analyses of dialyzable tuberculin components of B.C.G. culture filtrates were made to ascertain if there was a correlation between the molecular weights of these materials, as determined by the sedimentation velocity method, and their relative rates of dialysis. A positive correlation was found to exist. Despite the low molecular weights of these substances, which had sedimentation velocities between 0.5 and 1.5 x 10^{-13}, they were still immunologically active, as Dr. Chaparas of LBP demonstrated by the Ouchterlony technique.

(5) Antimicrobial extracts from shellfish, prepared by Dr. Li of LVR, were analyzed to determine their molecular weights. Seven samples, having sedimentation constants of less than 2 were analyzed, apparent diffusion coefficients were computed, and the molecular weights were found to range from 1,000 to 10,000.

(6) A series of eight sucrose density gradient experiments were performed on samples of immune rabbit sera submitted by Dr. Feeley of LBP in order to characterize and separate the immunologic components for further study. In addition, one sample was subsequently separated by gel filtration.

Significance to the program of DBS: Physical characterization of biological products is part of the basic information required for the DBS control and regulatory function and contributes also to the research program of the Division.

Proposed course of project: This project will be continued.

Part B included Yes /__/ No /X/

Serial No. DBS 29

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Simian virus 40. Electron microscopic studies of its relationship to rhesus kidney tissue culture cells.

Principal Investigators: John M. Easton, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1.60
Professional: 1.30
Other: 0.30

Project Description:

Objectives: To study the interrelationship between SV-40 and the rhesus kidney tissue culture cells in which it grows, using the electron microscope in addition to conventional tissue culture methods.

Methods Employed: The electron microscope is used to examine both naturally and artificially infected rhesus cell cultures, to locate viral particles in infected cells. Various modifications in the cell-virus environment, such as incubation at suboptimal temperatures or prolonged incubation, are studied in relationship to their ability to influence the yield and cytopathic effect of SV-40.

Major Findings: SV-40 multiplied slowly but progressively in cultures of primary rhesus kidney. Titers as high as 10^9 $TCID_{50}$ per culture supernatant (6 ml) were reached several weeks after initiation of infection. Production of high viral titers was accompanied by degeneration of the cell sheets. Electron microscopic examination of infected cells did not reveal characteristic viral particles until several weeks after infection. One continuous cell strain, $LLCMK_2$, supported the growth of SV-40 in a manner similar to that of primary cells. Another such strain, MS, did not support SV-40 multiplication measurably, and did not degenerate because of SV-40 infection.

Significance to the DBS Program: The study of the relationship of SV-40 to rhesus kidney cells is important because of the use of these cells in viral vaccine production, and the frequency of SV-40 contamination of such cultures.

Proposed Course of Project: Project will terminate on June 30, 1964.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part B Honors, Awards, and Publications

Easton, J. M.: Electron microscopic observations of simian virus-40 in primary rhesus kidney tissue cultures. Proc. Soc. Exptl. Biol. Med. 114: 663-665, Dec. 1963.

Serial No. DBS 30

1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Development of methods for the chemical analysis of biological products.

Principal Investigator: Jerome J. Helprin, Ph.D.

Other Investigators: John R. Miller, B.S., Harry P. Marshall, B.S.

Cooperating Units: None

Man Years:
Total: 2.5
Professional: 1.0
Other: 1.5

Project Description:

Objectives: To develop methods of chemical analysis of biologicals and to obtain typical analytical values for control, trouble-shooting, and research on these materials.

Methods Employed: Standard methods of chemical analysis are used, evaluated, or modified as required for the material being analyzed, and new methods are developed.

Major Findings: (1) A battery of non-destructive analyses of vaccines has been undertaken, to determine chemical consistency among lots for a product of one manufacturer, and between the same vaccines prepared by different manufacturers. The analyses consisted of specific conductivity by conductivity meter, pH by glass electrode, sodium, chloride, and cation concentrations by ion-specific glass electrodes, and ultraviolet and visible absorption spectra, on vaccines against poliomyelitis, typhus fever, mumps, influenza, rabies, cholera, measles, yellow fever, typhoid and paratyphoid fevers, pertussis, and Rocky Mountain spotted fever. This work provided base lines for subsequent analyses, and trained personnel in the use of the appropriate methods. In addition, it was gratifying to find that the methods were able to detect, in retrospect, a change in the concentration of buffer in the poliomyelitis vaccine of one manufacturer.

(2) Nitrogen analysis of these vaccines and related materials is performed by the classical Kjeldahl method. This one analysis is probably the most fundamental chemical measurement of the amount of biologically active material present. A total of about 66 analyses were performed on 21 different vaccines or fractions thereof, but because of the large amount of time consumed in this assay and the high accuracy and precision required, automatic equipment for performing the analysis is desirable.

(3) Methods of analysis of biologicals for heavy metals, especially lead and mercury, have been studied. A method was developed in which the metal is precipitated as the sulfide by thioacetamide. The precipitate is filtered onto a membrane filter which is then rendered transparent by treatment with microscope immersion oil. A holder was designed and fabricated to permit spectrophotometric determinations of the optical density of these disks. It was found that as little as 5 ppm of lead could be detected by this method. Similarly, 10 ppm of mercury could be detected. The method could not be used for cadmium analyses, however, because of the yellow color of the sulfide. Furthermore, since heavy metals were bound by protein, its presence, as in a vaccine, required that the protein be digested to release the metals before the analysis could be performed. It was concluded that the heavy metal and related elemental analyses will require the speed, sensitivity, and specificity which an atomic absorption spectrophotometer provides.

(4) Methods of analysis for inactivating agents and preservatives in biologicals have been studied, and a test for phenol is being developed which is simpler and faster than the methods commonly employed. The method takes advantage of the intense absorption

by phenols at 269 mu in the ultraviolet spectrum. Subsequently, the product of reacting the unknown with feric chloride gives a blue complex having an absorption peak in the visible spectrum which is characteristic for each phenol and differentiates phenol from substituted phenols such as cresol or tyrosine.

(5) Infra-red spectrophotometry is being investigated to determine if it will be suitable for the chemical analysis of biologicals. Because of the aqueous state of these materials the absorption in the infra-red spectrum by water tends to obscure the absorption by the other components. However, insufficient experience with this method precludes a firm opinion as to its utility at this time.

Significance to the program of DBS: The significance of this work lies in its potential for increased knowledge of the chemical composition of biologicals which can be of value in research thereon, and in increased surveillance of these products for the protection of the public.

Proposed Course of Project: This project will be continued.

Part B included Yes /__/ No /X/

Serial No. DBS 31
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Attempts to cultivate animal viruses in bacterial cells.

Principal Investigator: Jerome J. Helprin, Ph.D.

Other Investigators: None

Cooperating Units: Section on Respiratory Viruses, LVR

Man Years:
Total: 0.5
Professional: 0.5
Other: 0

Project Description:

Objectives: To determine the feasibility of culturing animal viruses in bacterial cells.

Methods Employed: Cell walls are removed from various species of bacteria by treating the bacteria with lysozyme. Suspensions of the remainder of the cells (protoplasts) are inoculated with virus and subsequently examined for evidence that they have been infected by the virus.

Major Findings: It was considered possible that changes in the respiration of protoplasts might indicate that they had been infected by a virus. Heavy suspensions of Aerobacter aerogenes were prepared, and standardized so that a 1:5 dilution had an optical density of 1.0 at a wavelength of 660 mu. A typical suspension had a dry weight of 1.3 mg/ml, a count of $10^{9.4}$ cells/ml, and a QO_2 of 170. A method was developed to prepare protoplasts from such cell suspensions by treating the cells with lysozyme. The respiration of the protoplasts was measured in the Warburg apparatus; no change in the respiration rate could be observed when influenza virus was added to the protoplasts. Since the protoplast: virus ratio was about 1000:1 it was felt that this ratio was too high and would have to be lowered by using a higher titer virus suspension before it would be possible to measure a change in the respiration rate.

Significance to the program of DBS: The significance of this work lies in the development of simpler methods for the propagation of viruses, which could be of value in both the preparation and testing of virus vaccines. Methods employing normal animal tissues for the growth of viruses have disadvantages which range from the presence of viruses potentially pathogenic for man to the technical problems inherent in the cultivation of animal tissues in vitro. If it can be demonstrated that an animal virus can be grown in a bacterial cell, then many of the disadvantages of animal tissue culture could be avoided.

Proposed course of project: This project has been temporarily discontinued.

Part B included Yes /__/ No /X/

Serial No. DBS 32
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Genetic variation in bacteriophages

Principal Investigator: Nobuto Yamamoto, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 0.75
Professional: 0.75
Other: 0

Project Description:

Objectives: To investigate the sharing of genetic information by serologically unrelated bacteriophages.

Methods Employed: The serologically unrelated bacteriophages P22 and P221 are compared as to phenotypic characteristics and are cultivated under conditions designed to favor emergence of mutants with properties which will reveal their genetic relationship to the normal forms.

Major Findings: In the course of a recombination experiment with P22H and P221 phages, an unusual hybrid, P22-221Hy was found. It mutates to P221 and P22S at frequencies of 10^{-4} and 10^{-5} respectively. Unlike P22h, P22S gives clear plaques on both S. typhimurium, St, and its mutant, St/22, but is morphologically and serologically indistinguishable from P22 and P22h. The use of single-clone technique on P22-221Hy proved that a P22-221Hy genome consists of a P22h and a P221 genome and is carried by the P22h capsid. However, it seems probable that the information for synthesizing the P221 capsid may be suppressed by the information for synthesizing the P22h capsid. P22-221Hy is a stable hybrid rather than a heterozygote, because it does not segregate by passing through host cells. Thus, one bacteriophage can carry the genetic information for two distinct bacteriophages.

Significance to the Program of DBS: None

Proposed Course of Project: This project will be discontinued.

Part B included Yes /X/ No /__/

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Yamamoto, N.: Bacteriophage: An unusual hybrid of serologically unrelated phages P22 and P221. Science 143: 144-145 (1964).

Honors and Awards relating to this project: None

Serial No. DBS 33
1. Laboratory of Biophysics and Biochemistry
2. Research Section
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 to June 30, 1964

Part A

Project Title: Physical and chemical characterization of viruses.

Principal Investigator: John F. Thiel, B.A.

Other Investigators: Bernice E. Eddy, Ph.D. (OD), Joseph P. O'Malley, M.D. (LVR), John C. Feeley, Ph.D. (LBP), Lewellys F. Barker, M.D. (LVR)

Cooperating Units: Office of the Director (OD), Laboratory of Virology and Rickettsiology (LVR) and Laboratory of Bacterial Products (LBP), all in Division of Biologics Standards.

Man Years:
Total: 1.50
Professional: 1.50
Other: 0

Project Description:

Objectives: To obtain information about the physical dimensions and chemical composition of animal viruses and to correlate this information with biological properties.

Methods Employed: Electron microscopic techniques for examining viruses in suspension or in situ in cells are supplemented by specialized techniques for concentrating and purifying viruses.

Major Findings: (1) Bizarre particles in tissue-culture cell debris. Sediments from centrifugation of tissue cultures from various sources were prepared for observation by Dr. Eddy. Negative staining of the sediments from HeLa cells, rabbit kidney cells, Japanese quail cells, and a continuous line of cercopithecus monkey kidney cells consistently revealed the presence of phage-like particles resembling those described by Dalton and Maloney in specimens prepared from the blood of leukemic mice and rats. The particles which we observed, however, were believed to be artefacts of cellular origin exposed by the negative staining procedure.

(2) Electron microscopic examination of cells infected with A-1 virus. Eleven samples of tissue-culture cells infected with A-1 virus were submitted by Dr. O'Malley. Examination of stained sections and negatively-stained particles from extracellular fluids failed to provide clear evidence for the presence of virus although there were consistent slight differences between the infected cells and normal cells from the same lot.

(3) In assistance to Dr. Feeley, the classical strain of cholera was studied in the electron microscope and compared with freshly-isolated bacteria suspected of being non-vibrio cholera. Cholera organisms could be detected among the varied flora recovered from fecal specimens.

(4) Specimens of typhus rickettsia prepared by Dr. Barker were examined to determine the extent of disruption following mechanical vibration. The series of micrographs disclosed that it was possible to control the final state of disruption by the extent of vibration.

Significance to the Program of DBS. Physical and chemical characterization of microorganisms used for vaccine production and of the adventitious agents which may contaminate the products provides information important for the control of vaccines.

Proposed Course of Project. This project will be continued.

Part B included Yes /__/ No /X/

Report of the
Laboratory of Blood and Blood Products
Division of Biologics Standards
January 1963 through June 1964

Summary of Research Activities: The research program of the Laboratory of Blood and Blood Products has included studies of the stability of blood products, as well as methods and standards for these products, blood banking equipment, red cell antigens and plasma antibodies, the clotting and fibrinolytic systems, and the proteins of body fluids. These various fields of interest have as their goal the improvement of procedures used for the control of the purity, potency and safety of biological products derived from blood. Thus the projects are directed not only toward improving existing control tests and developing new ones, but also toward providing stability data leading to more realistic dating periods for such products.

Studies of the stability of both Normal Serum Albumin (Human) and human gamma globulin during storage have been carried out. Information derived from the latter study has already been used in the preparation of Additional Standards for Measles Immune Globulin (Human) and has been considered in writing the initial drafts of Technical Standards for Poliomyelitis Immune Globulin (Human) and Immune Serum Globulin (Human).

Investigations of blood clotting have dealt with several phases of this complex biochemical process. In the course of this work a procedure has been developed for preparing plasminogen-free human fibrinogen that is also free of the fibrin stabilizing factor and/or plasminogen-free human fibrinogen that is also free of both the fibrin stabilizing factor and a plasmin (fibrinolysin) inhibitor which is present to varying extents in all human fibrinogen samples. The latter preparation is of interest as a substrate in plasmin testing since plasminogen-free, inhibitor-free fibrinogen exhibits a constant sensitivity to plasmin, whereas the sensitivity of other fibrinogen varies from batch to batch.

Summary of "Extramural" Research and Other Activities: The primary function of the Laboratory is the control of the purity, potency and safety of blood and blood products. Approximately three-fourths of the total time of the Laboratory personnel is occupied by this function. Control activities include the inspection of licensed establishments, the investigation of possible violations of the Public Health Service Act, and the testing of samples of blood products submitted for release, licensure, or as result of inspections. The review of license applications, labels, and circulars and the development of Technical Standards for biological products prepared from blood constitute integral parts of the overall control activity. In support of these functions the Laboratory has conducted an Inspector Training Course.

The "extramural" program of the Laboratory is not formally organized in the sense of extramural programs of other Institutes. However, the nature of the control functions provides opportunities for numerous contacts with scientific staffs of outside organizations. For example, the Fourth Voluntary Blood Bank Evaluation has just been completed. Under this program participating laboratories perform extensive tests on replicate samples of blood and report their results. Of the 202 establishments licensed for Whole Blood (Human), 179 participated in this evaluation.

To supplement the research activities of the Laboratory and yield specific information necessary for the development of regulatory standards, five research contracts have been negotiated. The project titles of these five contracts are:

1) Hemagglutinin Levels of Normal Human Plasma.

2) a) Optimal Standards of Potency for ABO Blood Grouping Serums.

   b) Development of Standards for Anti-Human Serum to Detect ABO Sensitization.

3) Anti-Human Protein Serums for Specific Identification of Proteins by Diffusion Methods.

4) Reagent Red Blood Cell Reference Panel.

5) Laboratory Studies of the Purity of Plasma and Plasma Fractions Stored in Plastic Containers.

Serial No. 34

1. Laboratory of Blood & Blood Products
2. Blood & Blood Derivatives
   Coagulation
   Diagnostic Reagents
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1963 through June 1964

Part A.

Project Title: Preparation, Characterization, Stability and Potency of Blood Products.

Principal Investigators: John N. Ashworth, Ph. D.
John T. Tripp, Ph. D.

Other Investigators: David L. Aronson, M. D.
Joan F. Bennett, A. B.
Marietta Carr, B. S.
Rita Conroy, B. S. N. E.
Ann L. Dayton, B. S.
Moises Derechin, M. D., Ph. D.
John S. Finlayson, Ph. D.
Paul Greene, B. S.
Carl T. Kisker, M. D.
Catherine Knapp, B. S.
Edward H. Mealey, Ph. D.
Eleanor G. Morrison, B. S.
Michael W. Mosesson, M. D.
Robert M. Pennington, M. S.
Joan Roelands, B. A.
Robert C. Scheno, A. B.
Donna Williams, B. S.

Cooperating Units: Department of Defense; National Institute of Arthritis and Metabolic Diseases (Dr. Victor J. Marder), National Cancer Institute (Dr. Michael Potter).

Man Years:
Total: 9.2
Professional: 6.3
Other: 2.9

Patient Days: None

Project Description:

Section I. Applied Research

Subsection I. Stability of Blood Products

Objectives: To determine the changes in properties of blood proteins which occur during processing, storage and related treatments.

Methods Employed: a) As a continuation of the long-term storage studies on Normal Serum Albumin (Human), samples were held at 32° C., 5° C., and room temperature. At intervals ultracentrifugal, electrophoretic, viscosity and precipitation measurements were made. Studies utilizing column chromatography are in progress.

b) To fill in information not obtained in studies of the chromatographically and ultracentrifugally detectable changes in albumin stored for long periods of time (J. Clin. Invest. 39:1837, 1960), a few samples of Normal Serum Albumin (Human) have been stored at 32° C. and 5° C. for shorter periods. These were examined at intervals by anion exchange chromatography and, when indicated, ultracentrifugation.

c) To determine whether a change was needed in requirements for the stability of Normal Serum Albumin (Human), nephelometric measurements of various dilutions of albumin were made before and after heating at 57° C. and 60° C.

d) Samples of stockpiled bovine albumin were received from the Office of Civil Defense and tested for their ability to enhance red cell agglutination when used as diluents in Rh testing.

e) In order to learn whether 0.3 M glycine is the most suitable diluent for maintaining the heat stability of human gamma globulin, solutions of this protein were diluted with either 0.3 M glycine or 0.15 M sodium chloride and heated for various periods at 57° C. Gelation times and electrophoretic characteristics were measured.

f) Preceding the issuance of Additional Standards for Measles Immune Globulin (Human), information was required on the stability of measles antibody. In cooperation with other laboratories of the Division of Biologics Standards, samples of gamma globulin were received from the Department of Defense stockpile and the measles antibody content measured. In addition the poliomyelitis and diphtheria antibody levels as well as the heat stabilities of these preparations were determined.

g) Final testing of NIH dried reference serums for blood grouping, prepared under contract in 1960, is in progress to determine the optimal conditions for reconstitution and their suitability as standards.

h) Studies on the changes occurring in liquid human plasma stored in plastic containers under a variety of conditions were initiated. Methods being employed include gravimetric measurements, infrared spectroscopy, electrophoresis, immunoelectrophoresis and immunodiffusion.

i) It is hoped that, as a complement to information gathered in the projects listed above, methods can be developed to determine the age of blood and plasma by testing in vitro. Techniques explored include measurements of

hemoglobin content, hematocrit, red cell count, osmotic fragility, freezing point, and refractive index as well as serological tests for syphilis.

Major Findings. a) In confirmation of results obtained over the past eight years of this study, greater changes were observed in human albumin stored at room temperature or 32° C. than in albumin stored at 5° C.

b) The short-term study of human albumin revealed that storage at 32° C. for 3 to 24 months produces changes in the chromatographic elution pattern which, though detectable, are minimal compared with those seen after 5 years at this temperature.

c) Nephelometric measurements suggested that, while 5% albumin is intrinsically more heat-stable than 25% albumin, there should be a higher allowable limit (in terms of nephelometric units) of turbidity for 5% Normal Serum Albumin (Human).

d) All Civil Defense bovine albumin samples tested were found to be suitable for use as diluents; results of this study were communicated to the Department of Health Mobilization.

e) Heat stability of human gamma globulin was found to be greater when a 16.5% solution was diluted to 10% with 0.15 M sodium chloride than when it was diluted with 0.3 M glycine.

f) The amount and potency of gamma globulin in the Department of Defense stockpile was determined and the Department of Defense apprised of these results. The best gamma globulin was that prepared from fresh or salvaged liquid plasma. Of intermediate quality was gamma globulin prepared from once-dried, non-irradiated (ultraviolet) fresh or salvaged plasma. That prepared from plasma which had been both dried and irradiated was of still lower quality. This information has been used in the preparation of Additional Standards for Measles Immune Globulin (Human) and has been considered in the writing of the initial drafts of Technical Standards for Poliomyelitis Immune Globulin (Human) and Immune Serum Globulin (Human).

g) Certain of the dried serums show sufficient blood group antibody activity to permit their use as NIH reference preparations. Others are of insufficient potency and will be discarded or used for other purposes. Tests indicated differences in titer, protein concentration and protein distribution (measured electrophoretically) of samples obtained from various manufacturers.

h) When plasma in plastic containers was stored surrounded by air at 32° C. or room temperature, a weight loss and a decrease in antigenicity as determined by immunodiffusion against anti-human horse serum was observed. No change in weight occurred when the samples were stored immersed in water, but the weight increased when they were stored immersed in 70% alcohol. Permeability of the plastic containers to Serratia marcescens was demonstrated by culturing plasma after storage of samples in growing broth cultures of this organism.

i) This project was inactive during the period covered by this report.

Subsection 2. Development of Methods and Standards.

Objectives: To develop protein preparations for standardization of assay methods and to modify existing techniques so as to provide a basis for future control tests.

Methods Employed: a) Comparison of the partial thromboplastin test and the thromboplastin generation test for antihemophilic factor have been carried out on several preparations. Parallel studies were carried out by Dr. V. J. Marder of the National Institute of Arthritis and Metabolic Diseases. Further comparisons have been made of the antihemophilic factor contents of these preparations with those of freshly drawn plasma from populations of normal donors.

b) Attempts have been made to adapt the quantitative hemagglutination technique utilizing the Coulter cell counter to routine measurements of antigens and antibodies.

c) Production of horse anti-human serum and characterization of the material obtained has been undertaken to provide a standard serum for immunoelectrophoresis and immunodiffusion techniques.

Major Findings: a) There is reasonable correlation between the results of the partial thromboplastin test and the thromboplastin generation test, with no evidence of systematic error. However, a lack of parallelism between the assay behavior of the reference preparations and test samples in the partial thromboplastin test renders this method less useful. Results of the cooperative study with Dr. Marder were presented at the International Conference on Hemophilia held in Washington, D. C. in December, 1963.

Comparison of the antihemophilic factor contents of the reference preparations with those of fresh plasma revealed that though there is a moderately wide range of antihemophilic factor levels in the normal population, there is good agreement of tests carried out on successive days and with different population samples. Moreover, the antihemophilic factor levels of the reference preparations were sufficiently stable over the period studied to indicate the possible use of these preparations as standards. Reference preparations have been sent to several laboratories for evaluation by similar comparisons.

b) The Coulter cell counter technique has been found suitable for the measurements of agglutination by naturally occurring antibodies in saline systems; antiserums obtained from commercial sources have been used as controls in these tests. Adaptation to routine use is still in progress.

c) Twenty liters of pooled horse anti-human serum has been obtained, filtered to render it bacteriologically sterile, and stored as aliquots. Identification of the antibodies present is in progress.

Subsection 3. Blood Banking Equipment.

Objectives: To gather information regarding equipment which comes in contact with blood products, with the intent of developing more significant control procedures on blood and blood products.

Methods Employed: a) The interchangeability of plasma equipment produced by various manufacturers has been studied.

b) It is proposed to undertake a study of the sterility of plasma equipment and bacteria counts on the outside of blood containers.

Major Findings: a) In general, parts of plasma equipment produced by different manufacturers were found to be interchangeable; however, certain deficiencies in design were revealed by this study. A full report of results and recommendations is in preparation.

b) Inasmuch as these investigations have only been proposed, no experimental results are available. Preliminary studies have indicated the presence of high concentrations of microorganisms on the surface of containers of blood.

Section II. Basic Research.

Subsection 1. Red Cell Antigens and Plasma Antibodies.

Objectives: To develop methods for the preservation of antigenically intact red cells that can be used for reagent purposes and to explore new methods for the study of blood group antibodies.

Methods Employed: a) Storage of red cells has been carried out after addition of preservatives, freezing in liquid nitrogen, and/or freeze drying.

b) The use of bentonite as a carrier for group A and B specific substances to permit a method for blood grouping without intact red cells is being investigated.

c) A program has been initiated to attempt to produce antibodies to rare type red blood cell antigens in white mice which have been sensitized with incomplete Freund's adjuvent to produce ascites. If successful, the experiment should yield ascitic fluid of high antibody titer in considerable quantity.

Major Findings: a) and c) None.

b) It has been shown that A and B antigens are adsorbed on bentonite and do react with specific antibody. As yet, flocculation of coated bentonite particles by antibody has not been achieved. Reactivity has been demonstrated by the loss of titer of the antibody (as measured by conventional red cell agglutination) upon treatment with the coated particles.

Subsection 2. The Clotting and Fibrinolytic Systems.

Objectives: To purify and characterize components of these systems and to develop an understanding of their chemistry as a basis for more useful assay procedures.

Methods Employed: a) The pathway of conversion of human prothrombin to thrombin has been studied by column chromatography and acrylamide gel electrophoresis. In order that this conversion may be studied in a controlled system, the isolation of the enzyme, thrombokinase, has been undertaken.

b) Isolation and purification of antihemophilic factor is in progress, utilizing ethanol fractionation, bentonite adsorption of fibrinogen, salt fractionation, and various combinations of these methods. To obviate the necessity for hemophilic plasma as a substrate in antihemophilic factor assay, work involving chelation and gel filtration to prepare an artificially depleted plasma is underway.

c) Standardization of spectrophotometric assays for plasminogen and plasmin with casein substrates is in progress. The stability of streptokinase-activated plasmin during the periods of assay is being determined simultaneously.

d) Study of the chromatographic heterogeneity found in highly clottable human fibrinogen was continued to learn the basis for this heterogeneity, to examine the plasmin (and trypsin) inhibitor associated with even highly purified plasminogen-free fibrinogen, and to obtain a fibrinogen which could be a potential standard substrate.

Major Findings: a) Several intermediates have been found in the conversion of human prothrombin to thrombin. Considerable purification of human thrombokinase (which is present in vanishingly small amounts in normal plasma) has been achieved, and preliminary experiments indicate that its action is similar to that of bovine thrombokinase, which was isolated by an extramural investigator.

b) A preparation of antihemophilic factor, purified approximately 100-fold over fresh plasma, has been obtained. Initial results of the tests utilizing artificially-depleted plasma as a substrate in assays for antihemophilic factor are promising.

c) A fraction of casein has been isolated which is hydrolyzed by plasmin without evidence of a lag phase. Determination of the optimal assay conditions with this fraction as substrate is in progress.

d) A large number of biochemical and biophysical techniques revealed no difference between the two chromatographically separated fibrinogens, but the two fractions did show a difference in electrical charge as revealed by electrophoresis at pH 8.6 and 5.5. The plasmin-trypsin inhibitor was shown to be a competitive inhibitor by kinetic studies in a fibrin-plasmin system. It was demonstrated that the inhibitor was not fibrin stabilizing factor (fibrinase). A procedure employing frontal analysis and stepwise elution chromatography on DEAE cellulose was developed to prepare 1) plasminogen-free fibrin-

ogen that was also free of fibrinase (i.e., a suitable substitute for fibrinase-deficiency testing) and/or 2) plasminogen-free fibrinogen that was also free of both fibrinase and the plasmin inhibitor. The latter was shown to be a suitable substrate for plasmin assays, since inhibitor-free preparations made from several different batches of fibrinogen exhibited the same sensitivity to plasmin, whereas the sensitivity of starting fibrinogen, evidently owing to differences in inhibitor content, varies from batch to batch.

Column chromatography utilizing gradient elution revealed that some, but not all, animal fibrinogens exhibit a heterogeneity of the type demonstrated by human fibrinogen. Of the 13 species examined, horse and monkey fibrinogen showed the greatest chromatographic similarity to human.

Subsection 3. Proteins of Body Fluids.

Objectives: To complement available data on blood proteins with a reservoir of basic information on the properties of and methods suitable for use on proteins of blood and other fluids.

Methods Employed: a) In association with Dr. M. Potter,National Cancer Institute, study of proteins in body fluids of laboratory animals was continued. Agar gel electrophoresis has been used as the major tool, but immunoelectrophoresis, immunodiffusion, gel filtration, column chromatography, paper electrophoresis, ultracentrifugation and peptide mapping have been used as ancillary techniques.

b) An attempt to isolate a gamma globulin fraction first noted during studies on the chemical characteristics of blood group antibodies (J. Immunol. 87:56, 1961) has been initiated. Methods employed include precipitation with various reagents, gel filtration, preparative ultracentrifugation and DEAE cellulose chromatography (batch and column techniques).

Major Findings: a) Agar gel electrophoresis at pH 5.5 showed that the relative amount and nature of the major urinary proteins of normal inbred mice vary with strain and sex. Five electrophoretic phenotypes were observed in 19 strains. The constancy of the electrophoretic pattern among individual mice of a given strain demonstrated that this was a useful new genetic marker. The fact that, within a given strain, there is often a difference between the patterns of the sexes which can be abolished by castration and hormone therapy suggested that this is a suitable system for the study of hormonal effects on protein synthesis.

b) Very small amounts of this protein have been obtained in a purified condition, as determined by biophysical measurements. It is hoped that this material can be isolated in sufficient purity and yield to determine what relationship, if any, it bears to various proteins of gamma mobility isolated by other workers since our initial observation was made.

Significance of Research: The Laboratory of Blood and Blood Products is responsible for control of the purity, potency and safety of products derived from blood. Surveillance of potency involves not only the ability to carry out

and interpret accurate assays but also the possession of knowledge regarding the stability of biological products. The applied research program and certain phases of the basic research program fill these needs by improving the validity and precision of potential control tests and by providing stability data leading to more realistic dating periods. In addition, the basic research program provides the professional staff with a constantly updated pool of fundamental information (including research methodology) necessary in evaluating new products and tests and in discussions with manufacturers.

Proposed Course of Project: Most of the various parts of this project will be continued. Tests of Department of Defense gamma globulin and bovine albumin, and of interchangeability of plasma equipment have been completed. Further investigation of fibrinogen heterogeneity is expected to be minimal. Final testing of NIH reference serums and the studies on the storage of albumin should be completed during 1964.

Part B included: Yes /x/ No /_/

PHS-NIH
Individual Project Report
January 1963 through March 1964

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Schmidt, P. J., Morrison, E. G., Solomon, J. M. $\mathfrak{Rh}_o$ (D^u) Testing with Anti-Rh_o' " (CDE) Reagents. Vox. Sang. 8: 242-244 (1963).

Aronson, D. L., Preiss, J. W., Mosesson, M. W. Molecular Weights of Factor VIII (AHF) and Factor IX (PTC) by Electron Irradiation. Thrombos. Diathes. Haemorrh. 8: 270-275 (1962). [Published too late to be included in 1962 project report.]

Finlayson, J. S. and Mosesson, M. W. Heterogeneity of Human Fibrinogen. Biochemistry 2: 42-46 (1963).

Mosesson, M. W., Finlayson, J. S. Biochemical and Chromatographic Studies of Certain Activities Associated with Human Fibrinogen Preparations. J. Clin. Invest. 42: 747-755 (1963).

Mosesson, M. W., Finlayson, J. S. Subfractions of Human Fibrinogen. Preparation and Analysis. J. Lab. Clin. Med. 62: 663-674 (1963).

Finlayson, J. S., Mosesson, M. W. Chromatographic Heterogeneity of Animal Fibrinogens. Biochim. Biophys. Acta 82: 415-417 (1964).

Williams, A. M., Finlayson, J. S., Tews, J. K. Effects of Glucose and Oxygen on the Metabolism of Glycine by Ehrlich Ascites Tumor Cells In Vitro. Biochim. Biophys. Acta. 74: 24-32 (1963).

Finlayson, J. S., Potter, M., Runner, C. R. Electrophoretic Variation and Sex Dimorphism of the Major Urinary Protein Complex in Inbred Mice: A New Genetic Marker. J. Nat. Cancer Inst. 31: 91-107 (1963).

Report on Other than Research Activities
Laboratory of Blood and Blood Products
Division of Biologics Standards
January 1963 through June 1964

Under the basic authority of the biological products provisions of the Public Health Service Act, the Laboratory of Blood and Blood Products of the Division of Biologics Standards has carried out its primary function of controlling the safety, purity and potency of blood and blood products. Table I and Table II indicate some of the functions performed as part of the laboratory's control activities.

1) Table I shows that 1544 man days were spent in performing investigations of possible violations of the Public Health Service Act and on site inspections of licensed establishments as required by regulations. Of these, 982 man days were during the 1963 calendar year. One investigation has resulted in the conviction of three defendants accused of the illegal interstate shipment for sale of blood plasma not manufactured in a licensed establishment. Appeals by the defendants to the Appellate and U. S. Supreme Courts were denied. As a result of other investigations two cases are awaiting trial in U. S. courts.

At the beginning of this report period there were 11 qualified inspectors and 7 trainees available to perform this work. Since that time 4 of the trainees have become qualified inspectors.

2) Table II shows the control testing that has been carried out on the blood and blood products produced by 223 licensees operating 294 principal locations and 235 donor stations and subsidiary facilities. The combined yearly production of Whole Blood (Human) alone of these establishments is in excess of four million units. The control testing of the 4385 lots (2841 during calendar 1963) submitted for release, licensure or as a result of inspections, includes the physical, chemical, and immunological testing as well as the review of manufacturers' protocols necessary as a basis for appropriate action. In excess of 30,000 tests were performed on these products.

3) Associated with the control testing program were the following:

a) License applications for 81 blood products were reviewed and the licenses were granted. Fifteen licenses were granted for establishments to produce blood and blood products. There are 16 licenses pending.

b) Over 420 groups of labels and circulars for blood products were reviewed for compliance with the regulations.

c) Regulatory Standards for Measles Immune Globulin (Human) were completed and became effective August 1, 1963. Technical Standards for Immune Globulin (Human) and Poliomyelitis Immune Globulin (Human) have been developed and are awaiting further action. Tentative Technical Standards for Anti-Human Chorionic Gonadotropic Serum and Blood Grouping and Typing Serum have been completed and will be submitted for comment.

d) The panel of typed donors composed of NIH employees, which is maintained as a source of extensively characterized red cells for use in the control and research program of the Laboratory, was increased from 480 to 650 members. This increase was the result of drawing and testing blood from an additional 455 NIH donors.

e) Under a training agreement approved by the Civil Service Commission a series of 40 lectures was given in the Inspector Training Course held for seven trainees and attended for refresher purposes by other qualified inspectors. The majority of the lectures were given by the senior staff members of the Laboratory. Invited lecturers included representatives of academic institutions, blood products manufacturers and other governmental control laboratories.

f) Tabulation of the results from the Fourth Voluntary Blood Bank Evaluation is currently in progress. Of the 202 establishments licensed for Whole Blood (Human), 179 participated in the evaluation. The laboratories of three State Health Departments and one City Health Department acted as referees in testing the blood samples that were distributed to the 179 blood banks.

4) To supplement the research activities of the Laboratory and yield specific information necessary for the development of regulatory standards, five research contracts have been negotiated. The project titles of these five contracts are:

1) Hemagglutinin Levels of Normal Human Plasma

2) a) Optimal Standards of Potency for ABO Blood Grouping Serums

   b) Development of Standards for Anti-Human Serum to Detect ABO Sensitization

3) Anti-Human Protein Serums for Specific Identification of Proteins by Diffusion Methods

4) Reagent Red Blood Cell Reference Panel

5) Laboratory Studies of the Purity of Plasma and Plasma Fractions Stored in Plastic Containers.

Over 450 man days have been spent by laboratory personnel in preparing reagents and developing specifications in support of the above research contracts. The development of a complex aseptic plasma pooling system, supervision of production of specified antiserums and labeling and distribution of hundreds of vials of human plasma fractions are illustrative of the supportive work performed.

Under consideration at the present time are the following contracts:

1) Coagulation Reference Products

2) Potentiation of Red Cell Agglutination by Macromolecules

3) Quantitative Separation of Agglutinated Red Cells from Unagglutinated Red Cells by Magnetoelectrophoresis

4) Effects of the Arm Preparation and Donor Bacteremia on the Safety of Blood

Summaries of Certain Control Activities
Laboratory of Blood and Blood Products
Division of Biologics Standards
Jaunary 1963 - June 1964 *

TABLE I
CONTROL ACTIVITIES REQUIRING TRAVEL STATUS

Type of Activity	Locations Inspected	Investigations Conducted	Contracts Undertaken	Man Days of Travel	
Annual Inspections	531 (294)			855 (500)	1544 (982)
Investigation of Possible Violations		13 (9)		689 (482)	
Supportive of Contracts			5 (4)	45 (35)	
				1589 (1017)	

* Figures in parentheses are values for calendar 1963.

Summaries of Certain Control Activities
Laboratory of Blood and Blood Products
Division of Biologics Standards
Jaunary 1963 - June 1964 *

TABLE II

CONTROL TESTING OF BLOOD AND BLOOD PRODUCTS

Type of Product	Number of Lots Tested			
	Inspection Samples	For License	For Release	Total
Blood Derivatives	6 (6)	23 (20)	1152 (753)	1181 (779)
Diagnostic Serums	274 (145)	92 (66)	1608 (1065)	1974 (1276)
Reagent Red Blood Cells		21 (14)	343 (232)	364 (246)
Whole Blood, Plasma, Packed Red Cells	776 (490)	90 (50)		866 (540)
	1056 (641)	226 (150)	3103 (2050)	4385 (2841)

* Figures in parentheses are values for calendar 1963.

LABORATORY OF CONTROL ACTIVITIES

This laboratory is responsibile for activities dealing directly with licensed establishments in relation to the licensing and control of biological products. It is supported by sections on control tests, pyrogens, and reference standards.

Its activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of the integrity of management and technical personnel, the physical facilities for manufacturing and testing of products, the scientific and professional qualifications of personnel and the evidence developed by manufacturers and the Division of continued safety, purity, and potency of products, for which an application for license is being evaluated. License applications are reviewed individually when required by an ad hoc committee consisting of appropriate members of the staff of the Division.

(b) Supervision of annual and special inspections of licensed establishments and of those for which an application for license has been made.

(c) Releasing of individual lots of biological products for distribution by manufacturers on the basis of review of manufacturers' and of DBS tests and of any other available information relating to the safety, purity, and potency of the lot of the product.

(d) The establishment and distribution of physical biological standards, reference preparations, and control materials. A small culture collection is also maintained mainly for the Division and for licensed manufacturers.

(e) Review of requirements and regulations now in effect for such constructive revision as needed and the development of requirements and regulations for new products.

(f) Maintenance of close working relations with other laboratories of the Division and other agencies to insure continuous knowledge of information needed for the licensing of establishments and new products and for the testing, release, and control of products already licensed.

The scope of activities carried out by this Laboratory is indicated by the fact that during the twelve month period, January 1, 1963 - December 31, 1963 a total of 7,248 control tests were carried out to insure the sterility, safety, potency and purity of licensed biological products as follows:

Products for Release	6,146	tests
Inspection Samples	1,038	"
Complaint Investigations..	64	"
Total	7,248	"

These results served as a basis for the release or rejection of individual lots of products. In addition 1,388 cooperative service tests were done on biological products not licensed.

During the same period 4,850 lots of biological products were submitted for release by licensed manufacturers. Of these 4,737 lots were released, 49 lots were rejected and 64 lots were withdrawn from consideration for release by the manufacturer.

To maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing, it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were: antitoxins - 14, serums - 3, vaccines - 2, toxoids - 2. A total of 708 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal potency tests and a number of specialized tests for specific products.

Standards, reference preparations, and cultures are freeze-dried for greater stability during storage. The following were dried between January 1, 1963 and December 31, 1963.

Cultures	4,232	Ampules
Serums	118	"
Vaccines	3,205	"
Viruses	1,295	"
Total	8,850	"

Official standards, reference, and control preparations currently maintained include 80 items.

Standards, reference preparations, and cultures were distributed to research or control laboratories of licensed and other manufacturers, health departments, and universities in this country and abroad as follows:

Antitoxins	378
Serums	2,761
Vaccines	931
Toxins	298
Bacterial & Viral Cultures	1,584
Total	5,952

Serial No. DBS 35
1. Control Activities
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report

Part A.

Project Title: Office of Chief, Laboratory of Control Activities

Principal Investigator: Dr. W. G. Workman (Jan. to June, 1963)
Vacant (June to Dec., 1963)

Other Investigators: None

Cooperating Units: Three

Man Years:
Total: 2½
Professional: 1/2
Other: 2

Patient Days: None

Project Description:

Under the direct supervision of the Director, Division of Biologics Standards, this Laboratory carries out activities directly with licensed manufacturers of biological products relating to their establishment and product licenses and to the control of biological products manufactured and distributed by them. These activities are supported by sections on reference standards, on control tests, and on pyrogens.

The activities include:

(a) Determination of eligibility of establishments and of individual biological products for license. This determination is made on the basis of a review of the integrity of management, of the physical facilities for manufacture and testing of products, of the scientific and professional qualifications of personnel, and of the evidence of continued safety, purity, and potency of products for which an application for license is being evaluated. Recommendations for establishment and product licenses are usually made by an ad hoc committee con-

sisting of appropriate members of the staff of the Division. The Chief of the Laboratory reviews such recommendations and processes licenses to be forwarded through Agency and Departmental channels for final approval.

A summation of license actions from December 1, 1962 through December 31, 1963 is as follows:

	Establishment	Product
Total Licenses Issued	24	129
Total Licenses Revoked	14	59

The total number of licenses in effect as of December 31, 1963 were 208 licensed establishments, 298 licensed products, and 1323 recorded product licenses.

(b) Supervision of annual and special inspections of licensed manufacturers and of establishments for which an application for license has been made. The total man days involved in inspections and investigations covering the same period as indicated above are as follows:

Annual inspections	610
Pre-license Inspections	31
Special Inspections and Investigations	481

(c) Releasing of individual lots of biological products for distribution by manufacturers on the basis of review of manufacturer's tests, of tests made in the Division, and of other data relating to the safety, purity or potency of other data relating to the safety, purity or potency of the individual lot of the product.

(d) The establishment and distribution of physical biological standards, reference preparations and control materials. A small culture collection is also maintained mainly for the Division and licensed manufacturers.

(e) Review of requirements and Regulations now in effect for such constructive revision as is needed and development of requirements and Regulations needed for new products. In addition, the Laboratory edits, maintains and issues various official documents and forms including Public Health Service Regulations, Additional Standards, Minimum Requirements of biological products, license application forms, as well as official memoranda to be directed to licensed manufacturers of biological products. As periodic revisions are made the documents are examined for suitability of design, format and conformance with both Agency and Departmental publication policies.

(f) Maintenance of close working relations between this Laboratory and the other Laboratories of the Division in order to insure continuous knowledge of all activities and information needed for licensing of establishments and of new products and for the testing, release and control of individual lots of products currently licensed.

(g) Serving on various committees and collaborating with other official or non-official agencies concerned with the manufacture, testing, control or use of biological products.

(h) Cooperation with other government agencies particularly the Department of Defense for interchange of information relating to the control of biological products and their use in preventive medicine.

(i) Maintains contacts with other workers in preventive medicine in this country and abroad.

Significance to Division of Biologics Standards: This project is directly related to the legal responsibilities and administrative functions of the Division, and requires close liaison with the research activities of the Division in order to put new knowledge to practical use.

Proposed Course of Project: It is proposed to continue the activities of this Laboratory as outlined except for coordinating the (1) inspection of licensed establishments and (2) licensing action which have been transferred to another office. Emphasis will be placed on improvements in control testing procedures, on the development and use of reference standards and on more useful requirements for products.

Serial No. DBS 36
1. Control Activities
2. Reference Standards
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1963

Part A.

Project Title: Investigations Related to the Establishment and Maintenance of Reference Standards for Biological Products.

Principal Investigator: E. B. Seligmann Jr., Ph.D.

Other Investigators: Miss Jane Farber
E. C. Russell
W. H. Berkeley

Cooperating Units: None

Man Years
Total: 7
Professional: 2
Other: 5

Patient Days: None

I. Project Description:

Objectives: Since most biological products cannot be standardized by chemical or physical means, recourse must be had to testing their effects in relation to physical reference preparations. It is the function of this project to provide these standard preparations for the use of manufacturers and others engaged in standardization in order to establish uniformity of potency throughout the country. It is largely by the use of these preparations that those portions of the biologics law relating to potency can be enforced. A great deal of painstaking and responsible work is necessary to insure that the preparations issued are satisfactory as official standard preparations for this country and bear a known relation to International preparations.

Methods Employed: Fluid preparations must be made and standardized from dried primary master standards prior to the expiration date of the current lot. Old standards must be replaced as they become exhausted. Standard preparations must be developed for new products and for certain of the older ones for which it has not been possible to prepare suitable preparations heretofore. This is dependent upon advanced knowledge in a number of fields, such as immunology, biology, biochemistry, and medicine and involves

bacterial and viral biological products, allergenic extracts and blood products. Important features of this work are the improvement of methods of preserving and storing standard preparations such as by freezing and drying, so that their potency may be maintained, selection or development of standard preparations which will yield clear-cut end points in control testing performed by all manufacturers, and correlation of these standards where possible with those established in other countries or with International Standards.

Major Findings and Accomplishments:

(a) In order to maintain an adequate supply of physical reference standards for use by the licensed manufacturers in their official control testing it is necessary to prepare and standardize new liquid lots from the primary dried stocks. The number of lots prepared and standardized during the year were antitoxins - 14, serums - 3, vaccines - 2, and toxoids - 2. A total of 708 tests were required to complete a satisfactory standardization of these lots. These tests include flocculation reactions, animal protection tests, animal titration tests, neutralization tests, and a number of specialized tests for specific products.

(b) Standard and Reference preparations and cultures are freeze-dried for greater stability during storage. This Section dried the following between January 1, 1963 and December 31, 1963:

Cultures	4232 ampules
Serums	118 ampules
Vaccines	3205 ampules
Viruses	1295 ampules
Total	8850 ampules

(c) This Section distributed to commercial houses, health departments, universities, and foreign countries the following Standard and Reference preparations:

Antitoxins	378
Serums	2761
Vaccines	931
Toxins	298
Bacterial & Viral Cultures	1584
Total	5952

(d) A culture collection of organisms used in the production and testing of biological products is

maintained by this Section. Official Standard, Reference and Control preparations currently maintained are listed on the attachment.

(e) Yellow Fever Vaccine manufactured under U. S. Government license has been tested for conformance to the official regulations governing its production. A total of 217 lots were tested for potency, 79 of which were tested for safety, during the year.

II. Proposed Course of Project:

An active research program is being pursued to provide basic data on the properties of existing and new standard preparations. A program designed to maintain a continuing evaluation of the stability of each physical standard preparation is in effect. The improvement of existing preparations is a subject of continual investigation. Research directed toward the establishment of physical standards for products not now provided with an official standard for the potency test is being pursued.

III. Proposed Projects:

Continuation of projects already in progress.

IV. Projects in Progress:

(a) Basic research on the cultivation and assay of various strains of vaccinia virus in chick embryo.

(b) Improvement of the stability of dried rabies vaccine.

(c) Development of an improved reference tetanus flocculating serum and toxoid.

(d) Development of an improved reference diphtheria flocculating serum and toxin.

(e) Development of a satisfactory dried diphtheria toxin for all laboratory assay purposes.

(f) Development of an improved opacity standard.

(g) Correlation of opacity standard with various types of bacterial suspensions used in production and challenge.

Part B included Yes [ ] No [X]

U. S. Standards

U. S. Standard Diphtheria Antitoxin

U. S. Standard Tetanus Antitoxin

U. S. Standard Histolyticus Antitoxin

U. S. Standard Oedematiens Antitoxin

U. S. Standard Perfringens Antitoxin (Welchii)

U. S. Standard Sordelli Antitoxin

U. S. Standard Vibrion Septique Antitoxin

U. S. Standard Type A Botulinus Antitoxin

U. S. Standard Type B Botulinus Antitoxin

U. S. Standard Staphylococcus Antitoxin

U. S. Standard Dysentery Antitoxin (Shiga)

U. S. Standard Pertussis Vaccine

U. S. Standard Tuberculin, Purified Protein Derivative

U. S. Standard Old Tuberculin

U. S. Standard Diphtheria Toxin for Schick Test

U. S. Standard Scarlet Fever Streptococcus Antitoxin

U. S. Standard Scarlet Fever Streptococcus Toxin

U. S. Standard Antirabies Serum

U. S. Standard Thrombin

U. S. Opacity Standard for Pertussis Vaccine

Reference Preparations

Reference Diphtheria Antitoxin for Flocculation Test

Reference Tetanus Antitoxin for Flocculation Test

Reference Histoplasmin

Reference Cholera Vaccine

Reference Plague Vaccine

Reference Typhoid Vaccine

Reference *Haemophilus influenzae* Typing Serum, Type a

Reference *Haemophilus influenzae* Typing Serum, Type b

Reference *Haemophilus influenzae* Typing Serum, Type c

Reference *Haemophilus influenzae* Typing Serum, Type d

Reference *Haemophilus influenzae* Typing Serum, Type e

Reference *Haemophilus influenzae* Typing Serum, Type f

Reference Haemophilus Influenzae Type b Antiserum

Reference Adenovirus Vaccine

Reference Influenza Virus Vaccine for CCA Determinations

Reference Influenza Virus Vaccine, Civilian Formula 1963

Reference Measles Serum

Reference Measles Virus Vaccine, Inactivated

Reference Measles Virus (Enders' Strain)

Reference Mumps Serum

Reference Poliomyelitis Vaccine

Reference Poliomyelitis Serum

Reference Attenuated Poliovirus, Lot TA2

Reference Attenuated Poliovirus, Lot TB2

Reference Attenuated Poliovirus, Lot TC2

Reference Attenuated Poliovirus, Lot NA2

Reference Poliomyelitis Immune Globulin

Reference Rabies Vaccine

Reference Smallpox Vaccine

Reference Typhus Serum

Reference Anti-A Blood Grouping Serum

Reference Anti-B Blood Grouping Serum

Reference Anti-Rh_o Blood Typing Serum

Reference Blood Group Substance A and B

Opacity Reference for Typhoid Vaccine

Opacity Reference for Cholera Vaccine

Reference for Nitrogen (Typhoid Vaccine)

Reference for Nitrogen

Control Preparations

Control Botulinus Toxin, Type A

Control Botulinus Toxin, Type B

Control Histolyticus Toxin

Control Oedematiens Toxin

Control Perfringens Toxin

Control Sordelli Toxin

Control Staphylococcus Toxin

Control Tetanus Toxin

Control Vibrion Septique Toxin

Supplement

Provisional Reference Type C Botulinus Antitoxin

Provisional Reference Antipertussis Serum

Provisional Reference Diphtheria Toxoid (Fluid)

Provisional Reference Diphtheria Toxoid (AP)

Provisional Reference Tetanus Toxoid (Fluid)

Provisional Reference Tetanus Toxoid (AP)

Control Adenovirus, Type 3, Strain JF

Control Poliomyelitis Virus, Type 1, Mahoney Strain

Control Poliomyelitis Virus, Type 2, Lansing Strain

Rabies Challenge Virus

Rabies Production Virus

Reagent Fibrinogen (Human)

Antimeningococcic Serum

Serial No. DBS 37
1. Control Activities
2. Pyrogens
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Section on Pyrogens

Principal Investigator: Harry W. Burruss

Other Investigators: None

Cooperating Units: None

Man Years
Total: 4 1/2
Professional: 1 1/2
Other: 3

Patient Days: None

Project Description

The primary responsibility of this section is the testing of certain licensed biological products to determine their safety, purity, and stability as defined in the control regulations under the Public Health Service Act. These biological products, especially the blood products of human and animal origin, are tested for pyrogenicity; their purity is determined in part by total solids content; and moisture determinations are made as a measure of stability of dried products. The principal products for pyrogen testing, which are submitted by licensed manufacturers for release, include streptokinase-streptodornase, vaccines, antivenins, antitoxins, blood albumin, globulin, fibrinogen, fibrinolysin, plasma, and serums.

During the year (January 1, 1963 through December 31, 1963) a total of 1090 samples were tested for pyrogenicity which required the use of approximately 3300 rabbits. This figure includes 584 samples submitted for release, 45 for the Laboratory of Blood and Blood Products, 333 pharmaceutical preparations for the NIH Clinical Center Pharmacy, 28 for the NIH Clinical Center Blood Bank, and 18 products for the NIH Media Department and Cancer Institute.

The principal investigator evaluated all pyrogen test results reported in the manufacturers' protocols to the Laboratory of Control Activities. On the basis of these evaluations and additional DBS tests on samples of the products submitted, recommendations for release or rejection were made. Records of all tests were maintained and officially reported.

Sixteen visiting scientists from domestic and foreign health laboratories and from licensed biological establishments were shown the techniques used in performing the work of this section. The Chief of this section also assisted in the annual inspection program of several licensed manufacturers. During the year several conferences were held with representatives of biological establishments on problems dealing with the pyrogen test.

Samples of each lot of Normal Human Serum Albumin released by the Laboratory of Control Activities continue to be distributed to different hospitals for clinical testing. Reports received on these lots of albumin confirm the reliability of the pyrogen test as a means of determining the safety of the product.

Studies were made to determine the test dose in rabbits on the pharmaceutical products for which no pyrogen test dose had been established.

Work is being done on the time of development and the duration of immunity (tolerance) to bacterial pyrogens in the rabbit. Reports in the literature are somewhat conflicting as to how long a rest period should be allowed the rabbits between tests.

A study was initiated to determine whether or not there is a significant difference in the pyrogen temperature responses in unrestrained rabbits tested by the hand-thermometer-lap method compared with the temperature responses in rabbits restrained in boxes with temperatures taken by an electronic thermometer with rectal thermocouples.

Control work in this section involves studies designed to adapt the above mentioned tests to new products, to study the factors influencing the test, and the adaptability of these tests as a means of evaluating the safety of experimental pharmaceuticals, including radioactive isotopes, under development by the NIH Pharmacy Department for clinical study in the NIH Clinical Center.

Part B included Yes /___/ No /X/

Serial No. DBS 38
1. Control Activities
2. Control Tests
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A.

Project Title: Control Testing and Investigations Related to Control of Biological Products.

Principal Investigator: Mr. Robert W. Kolb

Other Investigators: Mr. Otis L. Green
Vernon J. Fuller, Ph.D.
Mr. Harry T. Aylor

Cooperating Units: None

Man Years:

Total:	20.5
Professional:	4.0
Other:	16.5

Project Description:

The principal objective of this project is to assure the compliance of licensed biological products with standards established under the biologics control provisions of the Public Health Service Act. Individual lots of biological products are recommended for release on the basis of evaluation of the manufacturer's and Division of Biologics Standards tests. The evaluation includes control testing for sterility, safety, potency and purity as required for licensed biological products including antitoxins, therapeutic immune serums, blood and blood derivatives, bacterial vaccines, toxins and toxoids, multiple antigens, viral and rickettsial vaccines, diagnostic substances for dermal tests, antivenins, venoms and allergenic extracts. Supplemental to control testing are the following activities: (a) Evaluation of manufacturers' protocols of tests on lots of biological products for compliance with minimum standards; (b) preparation of releases; (c) maintenance of a permanent record and filing system for releases, protocols of manufacturers' tests, and samples of all biological products submitted to the Division and (d) a continuing reevaluation of methods and operations relative to the establishment of efficient control measures.

In addition to the above activities are a number of research and other functions which have been related to this program as follows: (a)

Research dealing with the development of new methods for the control of biological products and designed to improve existing in vivo and in vitro methods of testing; (b) research concerned with the study of stability of biological products and with the development and standardization of new biological preparations; (c) participation in the establishment and product licensing program, which involves the review and screening of new license applications, testing of products submitted in support of such applications, prelicensing inspections and preparation of official reports; (d) participation in the annual inspection program of licensed biological establishments and the control testing of inspection samples collected; (e) participation in the revision and formulation of regulations and additional standards for biological products; (f) cooperative investigations with intra-agency laboratories, commercial establishments, domestic and foreign governmental agencies in which studies and assays are carried out on numerous biological and pharmaceutical preparations; and (g) the orientation and training of new government personnel and visitors from other domestic and foreign health laboratories and institutions in biological control testing methods and related operations as conducted within the Division.

Major Findings and Accomplishments:

I. Control Testing Activities

(a) During the year (i.e., January 1, 1963 through December 31, 1963) biological products have been tested for conformance to Public Health Service standards and regulations. A total of 7248 control tests were carried out in the laboratory of Control Activities to insure the sterility, safety, potency and purity of licensed biological products. These are summarized as follows:

Products for Release.....	6146	Tests
Inspection Samples.....	1038	"
Complaint Investigations.....	64	"
Total	7248	

The data obtained served as the bases of recommendations for acceptance or rejection of the individual lots examined.

In addition, 1388 cooperative service tests were done on biological products not licensed.

(b) Permanent record and filing systems for releases, protocols of manufacturers' tests and samples of all biological products submitted to the Division of Biological Standards were maintained. During the same period indicated above 4850 lots of biological

products were submitted for release by licensed manufacturers. Of these 4737 lots were released, 49 lots were rejected and 64 lots were withdrawn from consideration for release by the manufacturers.

(c) Conducted 5 complaint investigations and 76 special actions or investigations of problems related to control activities during the past 15 months (January 1, 1963 through March 31, 1964). Written reports with recommendations for action as well as replies to informational inquiries were prepared for the Chief, Laboratory of Control Activities and Director of DBS.

(d) Evaluations of data collected in official potency tests run on rabies vaccines, smallpox vaccines, typhoid vaccines, cholera vaccines, and poliomyelitis immune globulins were made during the year. Tables were made for plotting the respective endpoint reactions obtained with the NIH reference materials in the various tests. Results showed that most of the potency assays conducted fell within 2 standard deviation limits.

This information has been helpful in studying variable factors in the test systems, in considering possible modifications or improvements in the laboratory control methods, and in keeping check on the continued stability and effectiveness of official reference standards.

II. Research

In addition to the above control testing, research experiments were carried out in conncection with the various projects under way. Brief summaries of these studies are given as follows:

(a) The cooperative study on the standardization of an official U. S. Reference Smallpox Vaccine was continued during the year.

Comparison of the potency assay method of the U. S. Reference Smallpox Vaccine by the rabbit scarification technique with a jet gun injection procedure on rabbits is complete and will be reported. The degree of potency obtained in the rabbit tests will be correlated with results obtained in current clinical field trials.

From results of these studies and an evaluation of manufacturer's data on further use of the proposed reference, it is anticipated that a final proposed revision of requirements for Smallpox Vaccine will be made available.

(b) Studies were continued on the development of potency methods for the assay of the fluid diphtheria component of Tetanus

and Diphtheria Toxoids Combined (For Adult Use). Experiments to standardize a reference toxoid preparation for use in guinea pig antigenicity assays were continued. A method for evaluating potency has been proposed but further trials and evaluations of commercial preparations are necessary before written standards for the product can be drawn up.

(c) A summary report was prepared of the experimental studies previously completed on the development and standardization of a reference diphtheria toxin for the Schick Test and the development of an accurate test procedure for this product. This report together with samples of the proposed reference toxin and a draft of requirements for the product were submitted to licensed manufacturers for examination and comment. As information is returned it is anticipated that a final reevaluation and revision of present requirements for the product will be made and a report of the studies will be proposed for publication.

(d) The development of a toxoplasmin potency assay in guinea pigs was initiated. The sensitizing agent is Toxoplasma gondii, RH strain, cultivated in mouse peritoneal fluid. Two types of skin test antigens were prepared, one derived from the peritoneal fluid of mice infected with toxoplasmata and the other from chicken embryos similarly infected. A report of the study will be made.

(e) In collaboration with the Laboratory of Bacterial Products and the Standards Section of LCA, studies have been initiated in which the animal potency of proposed DBS and International Reference Acetone-Killed-Dried (AKD) Typhoid Vaccines are being compared to the present phenolized, DBS typhoid reference vaccine. In addition, a study of the stability of the proposed DBS Reference Acetone-Killed-Dried vaccine is being conducted. At the completion of these studies a report will be made.

(f) DBS has been invited to participate in the international testing of a proposed International Reference Tetanus Toxoid, Adsorbed. This laboratory in collaboration with the Laboratory of Bacterial Products and the Standards Section of LCA is carrying out experiments in the testing of a proposed International Reference Tetanus Toxoid, Adsorbed and in comparing the potency of the International reference with various other tetanus toxoid preparations. The experimental data obtained will be correlated with those of other participating laboratories and will aid in the standardization of the international toxoid preparation as well as a potential DBS reference.

(g) Studies to develop a suitable animal potency test for coccidioidin, were initiated in collaboration with Dr. Harold Baer, LBP. A dried purified culture filtrate of Coccidioides immitis has been prepared and guinea pig sensitization experiments are in progress. A report will be made upon completion of this study.

III. Supportive Control Activities

(a) Numerous establishment and product applications were submitted for review and consideration for license. Usually these are referred to ad hoc committees for review. Personnel of this section participated in the review and processing of 12 establishments and 49 product license applications. Also, involved was the control testing of the products submitted in support of these license applications. Complete reports and recommendations were submitted on each application.

(b) Participated in the annual inspection program of biological establishments by carrying out 3 special and 40 regular inspections. Official reports and recommendations were made on all establishments visited.

(c) Participated in the drafting of requirements for Diphtheria Toxin for the Schick Test, Smallpox Vaccine, Allergenic Products, and Toxoplasmin during the current year.

(d) Three foreign visitors were given orientation and/or training in control testing and related activities during 1963.

IV. Proposed Course of Project

The proposed course is to continue the control testing, research and related programs with increasing efficiency and attempt to reach conclusions on both control and research projects in as satisfactory and expeditious manner as possible.

Part B.

Included Yes / / No /X/

Annual Report of the Laboratory of Viral Immunology

Division of Biologics Standards

During the eighteen months covered by this report the Sections comprising the reorganized Laboratory of Viral Immunology have maintained an active research program in vaccine-related fields and shouldered major responsibilities in the control of new biologic products.

Measles. The major effort of the Section on General Virology over the past several years has been devoted to acquiring information that would be useful in the development of live, attenuated and inactivated vaccines against measles. The first of these products was licensed in March, 1963 and there has now been over a year of general clinical use of both the live and "killed" vaccines. The Section has participated in a series of West African studies during which many questions relating to field use of the Enders "B" level attenuated strain have been resolved. These investigations involving vaccination of about one million children provided data which were extremely helpful in formulating the final requirements for the license of the live vaccine. Laboratory studies by the Section established standard methods for testing measles vaccines. The smooth transition from the period of research to license and subsequent general use of these vaccines testifies to the effectiveness of the Section in anticipating and meeting its research and control responsibilities in the measles field.

Rubella. Since the original reports of the isolation of rubella virus some two years ago a number of university and pharmaceutical groups have engaged in research activities that could ultimately lead to the development of vaccines. This past year the Section on General Virology responded to this general kindling of scientific interest by initiating a rubella research program as a major effort of the Section. Following the pattern set in the development of measles vaccines, the Division sponsored its first Conference on Rubella in April, 1964.

Smallpox. Smallpox continues to be a major health problem in much of the world and promises to be a constant threat to the United States and other smallpox-free areas for years to come. Maintaining an active smallpox research program, the Section on General Virology engaged in three clinical studies in the Republic of Upper Volta. This work provided information relating to the potency of vaccine in man as compared to several laboratory assay systems and data pertaining to jet inoculation of combined live smallpox, measles and yellow fever vaccines. These studies have opened several other promising avenues for exploration in the field of smallpox immunology.

Poliomyelitis. The Section on Viral Genetics has continued its research in the area of intratypic differentiation of poliovirus strains. This work and the application of "t" and "d" marker tests are extremely important in increasing our ability to predict by *in vitro* evaluation the

in vivo performance of various strains of attenuated polioviruses. These techniques apply directly to characterizing the virus strains incorporated in live vaccines and experimental strains that may be candidates for vaccine manufacture. Pursuing this approach, it may ultimately be possible to determine the specific chemical basis of virulence in polioviruses.

The Section on Serology has maintained a program of poliomyelitis research and control. New reference standards of poliomyelitis immune globulin and poliomyelitis hyper-immune serum have been assayed for neutralizing antibody content and made available as standard reagents. The research effort of the Section has centered on developing new and improved methods for testing the potency of inactivated poliomyelitis vaccines and poliomyelitis immune globulins. This work has been essential to the Division in meeting responsibilities in the control of poliomyelitis vaccine and globulin.

Latent virus studies. Since the discovery of SV_{40} in 1960 it has become clear that many, if not all mammalian and avian species harbor latent viruses, some of which may have an oncogenic potential. The complexities of this problem are enormous but of obvious importance in the field of biologics control since most virus vaccines are produced in mammalian or chick embryo cultures or in embryonated eggs. The Section on Viral Genetics has been engaged in a series of basic studies pertaining to viral latency using SV_{40} as the model agent. The results to date have made a valuable contribution to our knowledge of the mechanisms of viral latency and viral-induced malignant transformation of cells.

Study of genetic defects at the cellular level. With the increasing availability of diploid cell lines and developing interest in their use for vaccine production, there has been a corresponding accentuation in basic research programs using diploid cells. The Section on Serology has used this tool to demonstrate that the metabolic defect of Niemann-Pick disease exists on a cellular level and can be demonstrated in diploid cell cultures derived from patients. This type of investigation may provide a useful approach to the study of genetic influence upon cellular metabolism.

SUMMARY OF ANNUAL REPORT
FOR PATHOLOGY UNIT

The Pathology Unit has continued its work with testing of Poliovirus, Vaccines, Live, Oral. The greatest bulk of the testing has been of the Type 3 vaccines since this is the type about which there had been some concern. The need for monitoring this vaccine type has been apparent and the neurovirulence has been evaluated very carefully. In conjunction with Dr. Clifford Maloney, O.D., statistical analysis of neurovirulence data has been performed and certain acceptance levels for neurovirulence have been adopted.

Investigations are continuing in the study of the relationship of neurovirulence and *in vitro* characteristics of attenuated polioviruses.

Studies are also continuing in the field of viral oncogenesis and efforts are underway to alter animal susceptibility to tumor viruses.

The Pathology Unit has expanded its collaborative studies to include almost all the other laboratories of the Division and has had an increasing number of animal tissues to process and thus has had to increase its technical personnel by two. The unit foresees increasing responsibilities and collaborative efforts with other groups at DBS.

PHS-NIH
Individual Project Report
Fiscal Year 1963

Part A

Project Title: Neurovirulence Tests on Live Poliovirus Vaccines in Monkeys.

Principal Investigator: Ruth L. Kirschstein, M.D.

Other Investigators: Mr. Ronald Clark, Mr. George Rusten.

Cooperating Units: Serology Section screens monkey serums for freedom from antibody to poliovirus.

Man Years:

Total:	15.0
Professional:	0.5
Other:	14.5

Project Description:

Objectives:

To test Live Poliovirus Vaccines for ability to induce poliomyelitis in Rhesus monkeys when inoculated directly into the central nervous system.

Methods Employed:

Monkeys were inoculated with vaccine or dilutions thereof either intrathalamically or intraspinally, and observed for evidence of developing paralysis over a period of 17-18 days. The monkeys were then sacrificed and the central nervous system examined histologically for evidence of poliomyelitis. In addition tissues were saved for virus isolation attempts. This testing is performed as outlined by the PHS regulations for the Live Poliovirus Vaccines and test results were compared with similar results obtained with the reference vaccine preparations.

Major Findings:

The Reference Vaccine has been tested on 10 separate occasions during 1963 and the standards have thus been set and maintained. A total of 73 vaccine lots have been tested, the testing at present being performed on most of the vaccines submitted. In addition, certain seed virus lots have been tested. A total of 2905 monkeys have been

used in this testing. Of the lots tested, 15 have been Type I, 2 have been Type II and 50 have been Type III. On the basis of the findings of these tests, Type III Live Poliovirus Vaccine, Oral, has been well controlled. Evaluation of the qualitative differences seen in monkeys after Type III vaccine was made.

Significance to the Program of the Division: Integral part of the DBS program of control of Poliovirus Vaccine, Live, Oral.

Proposed Course: This endeavor will continue in 1964 on the same scale.

Part B included Yes /__/ No/X/

PHS-NIH
Individual Project Report
Fiscal Year 1963

Part A

Project Title: Monkey Safety Test for Poliomyelitis Vaccine and Adenovirus Vaccine.

Principal Investigator: Ruth L. Kirschstein, M.D.

Other Investigators: Mr. Ronald Clark, Mr. George Rusten.

Cooperating Units: Serology Section screens monkey serums for freedom from antibody to poliovirus.

Man Years:

Total:	3.0
Professional:	0.2
Other:	2.9

Project Description:

Objectives:

To test poliomyelitis and adenovirus vaccines for the presence of residual active virus particles that can only be detected by the direct inoculation of monkeys.

Methods Employed:

As outlined by the PHS regulations for the above vaccines.

Major Findings:

During 1963 and 1964, 3 of 54 poliomyelitis vaccines and 1 of 3 adenovirus vaccines were tested for safety in monkeys. The central nervous systems of 80 monkeys were examined grossly and microscopically. No histologic lesions were found in any monkeys.

Significance to the Program of the Division:

Integral part of the DBS program.

Proposed Course:

This endeavor will continue in 1964 on the same scale.

Part B Included Yes/__/ No/X/

PHS-NIH
Individual Project Report
Fiscal Year 1963

Part A

Project Title: Neurovirulence Tests on Measles Virus Vaccines in Monkeys.

Principal Investigator: Ruth L. Kirschstein, M.D.

Other Investigators: Mr. Ronald Clark, Mr. George Rusten

Cooperating Units: None

Man Years:

Total:	2.0
Professional:	0.1
Other:	1.9

Project Description:

Objectives:

To test Measles Virus Vaccines for the presence of neurotropic agents.

Methods Employed:

Monkeys were inoculated as outlined in the PHS regulations for the above vaccine.

Major Findings:

Twelve measles virus vaccines have been tested in 240 monkeys. No evidence of neurotropic agents has been found.

Significance to the Program of the Division:

Integral part of the DBS program of the control of viral vaccines.

Proposed Course:

It is expected that this endeavor will greatly increase in 1964.

Part B included Yes /__/ No /X/

PHS-NIH
Individual Project Report
Fiscal Year 1963

Part A

Project Title: The Pathogenesis of Infectious Diseases

Principal Investigator: Ruth L. Kirschstein, M.D.

Other Investigators: Dr. Alan Rabson, NCI
Dr. Joseph O'Malley, LVR-DBS
Dr. Harry Meyer, LVR-DBS
Dr. K.K. Takemoto, NIAID
Dr. Harold Baer, LBP-DBS
Dr. B.W. Uhlendorf, LVI-DBS
Dr. Robert Bowser, LBP DBS
Dr. Anthony Morris, LVR-DBS
Mr. Ronald Clark, LVI-DBS
Mr. Philip McGrath, LVI-DBS

Cooperating Units: Laboratory of Virology and Rickettsiology, DBS
Laboratory of Bacterial Products, DBS
Pathologic Anatomy Branch, NCI
Laboratory of Pathology, NCI
Laboratory of Biology of Viruses, NIAID

Man Years:

Total:	5.5
Professional:	0.2
Other:	5.3

Project Description:

Objectives:

Experimental infectious diseases are studied as to pathogenesis in the hope that this may further elucidate the pathogenesis of infectious diseases in man.

Methods Employed:

Infectious agents or related substances are injected into a variety of animals when newborn or adult and gross autopsies and histologic examinations are performed at timed intervals so that the development of the disease process and the pathologic changes may be studied.

Major Findings:

(1) (With Dr. Rabson) Studies on the comparative oncogenic effects of polyoma virus, simian virus 40, and adenoviruses are continuing. It has been found that polyoma virus produces tumors in mice, rats hamsters and mastomys, SV40 produces tumors only in hamsters, mastomys and adenovirus 12 and 18 produces tumors in hamsters, mastomys and certain inbred strains of mice.

(2) (With Dr. Rabson) Studies of the ability of the oncogenic viruses to "transform" hamster cells, human cells and monkey cells in cell cultures are continuing. The cellular transformation has characteristics of malignancies and has limited growth potential when inoculated into animals. Attempts to alter this growth potential are underway.

(3) (With Dr. Takemoto) Studies of the neurovirulence of plaque variants of attenuated polioviruses reveal no relationships between virulence and plaque size.

(4) (With Dr. Uhlendorf) Studies on the neuropathogenicity and oncogenic effects of all other simian viruses are in progress using fluorescence microscopy techniques as well as those discussed above.

(5) (With Drs. Baer and Bowser) Studies of the toxicity of poison ivy extracts reveal that these substances are not toxic for monkeys and that the monkeys can develop hypersensitivity.

(6) (With Dr. O'Malley) Studies of an agent (A-1) in monkeys are in progress to determine if these animals develop hepatitis. These studies include histologic examination of needle biopsies of the liver and blood counts as well as virologic and serologic determinations.

(7) (With Dr. Morris) Studies of an agent isolated from rabbits and causing death in suckling hamsters are in progress.

(8) (With Mr. Clark) Studies of the neuroanatomical development of various animal species are in progress.

(9) (With Mr. Clark) Studies of the sensitivity of finite neuroanatomical structures to virulent and avirulent poliovirus are in progress.

(10) (With Mr. McGrath) Cytologic examination of cell cultures infected with various viruses reveal that specific stains may be useful in determining the nature of the viral infection.

(Within the Section of Pathology, 33,766 histologic sections were cut and stained with gallocyanin, 6,000 with hematoxylin and eosin and 2,000 with special stains. This is roughly 375 slides per month per technician.)

Part B included Yes/X/ No /__/

Part B

Honors, Awards, Publications:

Takemoto, K.K. & Kirschstein, R.L., Dextran Sulfate Plaque Variants of Attenuated Type I Poliovirus; Relationship to In Vitro and In Vivo Markers. Journal of Immunology, 92:329. 1964.

Rabson, Alan S., Kirschstein, Ruth L. & Paul, Frances J., Tumors Produced by Adenovirus 12 in Mastomys and Mice. Journal of National Cancer Institute. 32:77. 1964.

Woods, W.A., Robbins, F.C., Weiss, R.A., Cashel, J. & Kirschstein, R.L. Characteristic of Sabin Type I Poliovirus after Gastrointestinal Passage in Newborn Infants. II. Antigenicity & Elution from $Al(OH)_3$ gel. American Journal of Hygiene. 79:236-243. 1964.

Serial No. 43

1. Laboratory of Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Immunological Studies of Attenuated and Virulent Polioviruses.

Principal Investigator: Dr. Paul Gerber

Other Investigators : None

Cooperating Units : None

Man Years:

Total	:	1.8
Professional	:	0.3
Other	:	1.5

Project Description: Part I. Intratypic antigenic analysis of polioviruses by cross neutralization tests with absorbed immune sera.

Objectives: To develop a simple method for the intratypic differentiation of attenuated and virulent strains of polioviruses.

Methods Employed: Immune sera to type I poliovirus (LSC or Mahoney) are absorbed with concentrated, inactivated heterologous virus. Intratypic cross neutralization tests were carried out.

Major Findings: The absorbed antisera against type I attenuated or virulent polioviruses reacted specifically with the homologous virus without any heterologous cross-reaction. This test enables us to detect small antigenic changes in vaccine viruses which may have a bearing on possible reversion toward greater virulence.

Significance of Program to the Division: This study contributes to our knowledge of the properties of attenuated polioviruses and the technique may be of importance in control tests of poliovirus vaccine.

Proposed Course: It is planned to extend this work to type III polioviruses.

Serial No. 43

Project Description: Part II. Determination of the possible immunochemical basis of neurovirulence of polioviruses.

Objectives: Attempt to demonstrate intratypic immunochemical differences between virulent and avirulent polioviruses.

Methods: Preparation of purified poliovirus antigens for use in quantitative complement fixation tests designed to detect antigenic differences.

Major Findings: No definite results have been obtained so far.

Significance of Program to the Division: To obtain basic information regarding the biological properties of polioviruses.

Proposed Course: Study is continuing.

Part B included yes / / no /X/

Serial No. 44

1. Laboratory of Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : In Vitro Tests on Live Poliovirus

Principal Investigator: Dr. Paul Gerber

Other Investigators : Mr. Joseph L. Rogers, Jr.

Cooperating Units : None

Man Years:

Total	2.5
Professional	0.5
Other	2.0

Project Description:

Objectives: To determine the genetic characteristics and the concentration of poliovirus present in samples of oral, live poliovirus vaccine and to detect extraneous agents in such preparations.

Methods Employed: The "t" and "d" marker tests were carried out by methods outlined in the scientific literature. The antigenic characters were determined by the intratypic serum differentiation test. Extraneous agents were searched for by neutralizing the undiluted poliovirus vaccine with specific high-titered antisera. This preparation was then inoculated into cultures of African green monkey kidney cells.

Major Findings: Seventy one samples of vaccine were tested. Seven lots of vaccine were found to contain extraneous viruses and were rejected. Three lots of vaccine showed changed genetic markers indicating reversion toward virulence. These too were rejected.

Significance of Program to the Division: This is an integral part of DBS control activities.

Part B included yes / / no /X/

Serial No. 45

1. Laboratory of Viral Immunology
2. Section on Viral Genetics
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Studies on Simian Virus$_{40}$.

Principal Investigator: Dr. Paul Gerber

Other Investigator : None.

Cooperating Units : None.

Man Years:

Total	:	1.5
Professional	:	0.5
Other	:	1.0

Project Description: Part I. Study of a persistent subviral infection in SV$_{40}$-induced hamster tumor cells.

Objectives: To study the phenomenon of viral latency.

Methods Employed: Conventional virologic techniques.

Major Findings: No virus is detectable in tumor cell extracts, however, the presence of subviral infectivity was indicated by formation of virus following seeding of intact tumor cells onto sensitive indicator cells.

Significance of Program to the Division: This study contributes basic information to our knowledge of latent virus infections.

Proposed Course: This project is continuing.

Part B Included yes /X/ no /__/

Project Description: Part II. Study of patterns of antibodies to SV_{40} in children vaccinated with poliomyelitis vaccine containing live SV_{40}.

Objectives: To determine whether the levels of antibodies to SV_{40} decrease or persist during 3-4 years after last vaccination.

Methods Employed: Sequential sera of children following their last known booster dose were assayed for SV_{40} neutralizing antibodies as well as for antibodies to poliovirus type II. The antibody patterns were then compared.

Major Findings: None of ten children vaccinated with Maitland type poliomyelitis vaccine developed significant antibody rises to SV_{40}. Of thirty children inoculated with vaccine prepared by the trypsinized cell culture technique, nine showed 4-fold or greater antibody rises to SV_{40}; in three of these the SV_{40} antibody levels persisted while the polio antibodies declined.

Significance to the Division: To obtain information on the effect of trace amounts of SV_{40} inoculated into children at the time of vaccination with poliomyelitis vaccine.

Proposed Course: Attempts will be made to obtain additional sera in order to extend the present findings.

Part B Honors, Awards, and Publications

1. Gerber, P; Tumors Induced in Hamsters by Simian Virus 40: Persistent Sub-viral Infection. (Science 140: 889-900, 1963)

2. Gerber, P; Studies on a Persistently "Masked" Viral Infection in Cells of SV_{40}-Induced Ependymomas. (Proc. Am. Assoc. Cancer Res. 4: 22, 1963)

Serial No. 46

1. Laboratory of Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Serologic Studies Concerning Poliomyelitis and Poliomyelitis Vaccines.

Principal Investigator: Mrs. Eva Rau Brown

Other Investigators : Dr. George A. Hottle
Dr. B. W. Uhlendorf
Dr. Ruth L. Kirschstein

Cooperating Units : None

Man Years:
Total: 5.0
Professional: 2.0
Other: 3.0

Project Description:

A. Establishment of poliomyelitis reference standards.

It has become necessary to evaluate the following new reference standards: (1) poliomyelitis immune globulin (P.I.G.), (2) poliomyelitis immune serum and (3) inactivated poliomyelitis vaccine (trivalent). The methods employed included the determination of polio neutralizing antibodies by the metabolic inhibition test (M.I.T.) and vaccine antigenic potency by inoculation of chickens and monkeys.

It was shown by paired sample analysis that the proposed new reference P.I.G. was not significantly different from the established standard for any of the three types of poliovirus neutralizing antibody. It has subsequently become the established standard.

Serial tests are being performed to collect sufficient data for a statistical evaluation of the reference serum and trivalent vaccine.

B. Evaluation of antibody content of poliomyelitis immune glubulin and immune serum globulin.

These two commercial preparations are released for human use on the

Part B Honors, Awards and Publications.

Uhlendorf, B. W., Brown, Eva R., Fabisch, Phyllis H., Hottle, George A: Standardization of Poliomyelitis Immune Globulin. J. Immunology, in press.

basis of (among other things) their neutralizing antibody content for type 2 poliovirus. For some years this test has been performed in mice, although a theoretically more useful procedure, the metabolic inhibition test (M.I.T.) was available.

In the current study, M.I.T. tests for neutralizing antibodies for all three types of poliovirus were performed on 185 lots of gamma globulin to determine the range of titers encountered in the commercial product. It was demonstrated that the polio antibody content of globulin lots of placental origin was far higher than that of globulins prepared from plasma pools. These data have been analyzed to provide a basis for revising the requirements for the polio antibody content of human gamma globulin.

C. Evaluation of poliomyelitis vaccine potency assay procedures.

For several years there has been a continuing evaluation of the procedures used for the potency assay of poliomyelitis vaccines. The test proscribed by the Regulations involves inoculation of monkeys on three separate occasions and subsequent study of their sera for antibody content. Another promising but unofficial procedure requires a single inoculation of chickens and later, serologic assay of their blood specimens for antibody.

A standard method has been devised for the chick test. Twenty chickens 38-days old each receive an intramuscular inoculation of a 1:4 dilution of the vaccine on test and are bled 96 hours later. This procedure is far less expensive and time consuming than the monkey test which requires that the animals be on test for 21 days and be given three inoculations.

An analysis of variance indicated that a vaccine assay employing 20 chickens should give slightly more reproducible results than an assay using 12 monkeys. A further analysis of these data is in progress and should provide more information concerning the reliability of the chick test system.

Significance to bio-medical research and the program of the Division:

All work on this project directly pertains to the responsibilities of the Division in the control of poliomyelitis vaccine and human gamma globulin.

Proposed Course:

This is a continuing project.

Part B included yes /X/ no / /

Serial No. 47

1. Laboratory of Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Study of Inherited Metabolic Disorders in Human Diploid Cell Strains (HDCS)

Principal Investigator: B. William Uhlendorf, Ph.D.

Other Investigators : Donald S. Fredrickson, M.D.
Albert I. Holtz, M.D.

Cooperating Units : National Heart Institute, NIH

Man Years:

Total	1.8
Professional	0.8
Other	1.0

Project Description:

Objectives: To determine whether the biochemical manifestations of inborn errors of metabolism persist in cell cultures derived from tissues of individuals with certain inherited diseases.

Methods Employed: 1) The initiation, serial propagation and preservation of euploid cell cultures; 2) chromosome studies; 3) thin layer chromatography; 4) quantitative chemical analysis for phospholipids, DNA, etc; 5) uptake of radio-isotope-labeled compounds.

Major Findings: Euploid cell culture-derived from tissues (bone marrow, skin and amnion) of three patients with Niemann-Pick (NP) disease and from thirteen control donors have been analyzed. As in the tissues of the patients the sphingomyelin content of the cultured NP cells is higher than that of the cultured cells. These results were presented at the "Federation Meetings" in Chicago, April, 1964.

Significance to Biomedical Research and to the Division:

These results suggest the application of tissue culture methods to the study of the metabolic basis of Niemann-Pick disease as well as other inborn errors of metabolism. These findings may also be important in the possible development of human diploid cell strains for vaccine production.

Proposed Course: This study will be continued and results will be published in the scientific literature.

Part B included yes /_/ no /X/

Serial No. 48

1. Laboratory of Viral Immunology
2. Section on Serology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Studies on Simian Viruses

Principal Investigator: B. William Uhlendorf, Ph.D.

Other Investigators : Ruth L. Kirschstein, M.D.
(sub-project #4 only)

Cooperating Units : None

Man Years:

Total:	3.0
Professional:	0.6
Other:	2.4

Project Description:

(1) Preparation and maintenance of simian virus pools and of specific antisera to these viruses.

With the addition of SV_{30}, SV_{31}, SV_{32}, SV_{34}, SV_{37}, SV_{41} and Foamy Types I and II we now have thirty six simian viruses. With the preparation of antisera to ten of these we now have a total of 25 specific antisera. The virus pools are being tested for possible contamination with SV_{40} but so far, only one has been found.

(2) Determination of the sensitivity of a new cell line derived from a monkey embryo.

A line of cells allegedly derived from a rhesus monkey embryo shows a good sensitivity to SV_{40} as well as to other simian viruses. Its species of origin is being determined by the technique of mixed cell agglutination.

(3) The isolation and identification of adventitious agents from cell cultures and from monkey CNS.

About twenty agents have been isolated. Of these, identifications of Poliovirus Types I and III, Foamy Type I and SV_5 have been made.

(4) Investigations of the possible oncogenicity of the simian adenoviruses.

Several of the Group I Simian viruses have been tested and one was found to be oncogenic for hamsters.

Proposed Course: Subprojects No. 2 and 4 are being continued, with intent to publish the results.

Part B included yes /__/ no /X/

Serial No. DBS 49
1. Viral Immunology
2. Tissue Culture
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on SV40 virus, an important adventitious agent of rhesus monkey kidney cell cultures

Principal Investigators: Dr. George A. Hottle
Dr. Donald McKinstry

Other Investigators: Brenda Abbott
Robert Grubbs

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1 1/4
Professional: 1/2
Other: 3/4

Project Description:

Objectives: (1) To study the factors determining the occurrence of SV40 in the kidneys of rhesus monkeys; (2) to improve diagnostic methods for the detection of this common adventitious agent.

Methods Employed: Samples of tissue culture fluid from primary rhesus monkey kidney cell cultures (after the medium change at 5 days and a holding of the overlay for 21 days without fluid changes) were subcultured into cercopithecus monkey kidney cell cultures and observed for cell degeneration for 14 days. The cultures exhibiting the cytopathic effect characteristic of SV40 were tested for the presence of this virus by passage and neutralization by the specific immune serum.

Leighton tubes were prepared from approximately 25% of the rhesus monkey kidney lots; the cover slips were stained with hematoxylin-eosin for intranuclear inclusion bodies characteristic of SV40 virus.

Major Findings: During the one year period of preliminary survey (January 28, 1963 to January 30, 1964), 102 lots of rhesus monkey kidney primary cell cultures were processed. Sixty-two percent of these lots were found positive for SV40 virus by subculture

and neutralization. Of the 23 lots checked by staining, 50 percent were found positive for intranuclear inclusion bodies characteristic of SV_{40}, as compared to 70 percent of the same lots positive by the subculture method.

Significance to Bio-medical Research and the Program of the Division: It is essential to keep it out of human vaccines whenever possible. The results above suggest that the rapid staining technique may be useful in screening out most of the SV_{40} contaminated lots without waiting for the subculture results.

Proposed Course of the Project: The project will be pursued further as time allows.

Part B included Yes/ / No/X /

Serial No. DBS 50
1. Viral Immunology
2. Tissue Culture Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Safety testing of killed virus vaccines in cell culture

Principal Investigators: Dr. George A. Hottle
Dr. Alexis Shelokov

Other Investigators: Robert Grubbs

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 2 1/6
Professional: 1/6
Other: 2

Project Description:

Objectives: (1) To determine the susceptibility of the several cell systems, under the prescribed test conditions, to polio-, adeno-, measles and SV_{40} viruses by means of pre- and post-sensitivity tests; (2) to test killed virus vaccines for safety using these cell culture systems.

Methods Employed: The methods are those outlined in the PHS regulations and the scientific literature.

Major Findings: During the calendar year 1963 samples of 11 lots of inactivated poliovirus vaccine (4 manufacturers), 8 lots of adenovirus vaccine (2 manufacturers), and 16 lots of measles vaccine (2 manufacturers), were tested for safety in tissue culture. All cell culture lots employed were found sensitive to polio-, adeno-, measles, and SV_{40} viruses. All of the vaccines satisfied the requirements of the tissue culture safety test.

Significance to Bio-medical Research and Program of the Division: This project fulfills a major statutory responsibility of the Division.

Proposed Course of the Project: This is a continuing project.

Part B included Yes/ / No/X/

Serial No. DBS 51
1. Virology Immunology
2. Tissue Culture
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Occurrence of pleuropneumonia-like organisms in serial cell cultures

Principal Investigators: Dr. George A. Hottle
Brenda Abbott

Other Investigator: Robert Grubbs

Cooperating Units: None

Man Years(computed for the 18 month period)
Total: 1 1/4
Professional: 1/4
Other: 1

Project Description:

Objectives: 1) To develop methods for elimination of pleuropneumonia-like organisms from serial cell cultures propagated in this Laboratory; 2) To study the occurrence of PPLO in serial cell cultures and to determine the effect of their presence on the biology of the cultured cells.

Methods Employed: Monkey stable cell cultures propagated in Eagle's basal medium (Hanks' base with 10 percent calf serum) were treated with different concentrations of tetracycline, kanamycin, tetracycline and kanamycin, sodium azide and beta-propiolactone. The cell cultures were transferred approximately once a week by trypsinization. At the time of transfer, the tissue culture fluid was subcultured onto PPLO agar and Barile's medium plates to check for PPLO growth. Cell cultures that showed no evidence of PPLO growth were placed on antibiotic-free medium for 21 days with weekly checks for PPLO.

Major Findings: The only technique (of the several employed) which consistently eliminated PPLO was the adding of 10 mcg/ml of tetracycline and 100 mcg/ml of kanamycin to the medium. By this means, all the fourteen serial cell lines regularly used at DBS were freed of PPLO contamination. They are available for distribution from this Section for vaccine testing and research uses by DBS staff.

Significance to Bio-medical Research and the Program of the Division: The PPLO organisms are a common contaminant of serially propagated cell lines. A simple and effective method for their elimination is a welcome addition to the armamentarium of tissue culture laboratories.

Proposed Course of the Project: Studies on the occurrence and detection of PPLO organisms in serial cell cultures will continue. Observations suggesting possible effects of these organisms on the cell and its response to viral infection will be pursued.

Part B included Yes/ / No/X/

Serial No. DBS 52
1. Viral Immunology
2. Tissue Culture Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Preparation of primary and serial cell cultures for research and vaccine test use

Principal Investigators: Dr. George Hottle
Dr. Alexis Shelokov

Other Investigators: Robert Grubbs

Cooperating Units: Monkey Safety Testing Unit, Animal Test Section, LVR, DBS

Man Years (computed for the 18 month period)
Total: 6 1/2
Professional: 1/4
Other: 6 1/4

Project Description:

Objectives: To prepare a variety of standard and experimental primary and serial cell cultures for research and testing of viral vaccines.

Methods Employed: Standard tissue culture techniques are used, including those designed or modified by this Section.

Major Findings: During this reporting period (January 1, 1963 to June 30, 1964) a total of 468,980 tubes, 155,723 two-ounce bottles, 6,261 milk dilution bottles and 4,066 32-ounce bottles of both primary and serial cell cultures was prepared by the Tissue Culture Section. Large quantities of rhesus, cercopithecus and BS-C-1 cell cultures were used to expedite the testing required for the release of live poliovirus, as well as live and killed measles vaccines. Several primary cell culture lots of guinea pig, hamster, dog and pig kidney were processed on special request from the interested investigators.

The pertinent cell culture information is summarized in Tables 1, 2 and 3.

Significance to Bio-medical Research and Program of the Division: These cultures, after appropriate check for cell growth and possible contamination, provide an indispensable tool for the fulfillment of the vaccine testing responsibility of the Division and for the use by research investigators in this and other laboratories of DBS and even certain other Institutes.

Proposed Course of the Project: This is a continuing project.

Part B included Yes [ ] No [X]

TABLE 1

Report for the Period

January 1, 1963 - June 30, 1964

CELL YIELD FROM PROCESSED ANIMAL TISSUES

Type of Tissue	Number Processed	Volume of Packed Cells (ml)
Kidney		
Monkey, rhesus	953	2,886
Monkey, cercopithecus	328	1,106
Rabbit	702	1,317
Guinea pig	12	8
Hamster	38	16
Dog	4	10
Pig	2	24
Embryo		
Chick	2,244	1,806
Mouse	564	112
Hamster	373	35

TABLE 2

Report for the Period

January 1, 1963 - June 30, 1964

NUMBER OF PRIMARY CELL CULTURES ISSUED

Type of Culture	Tubes	Bottles		
		2 oz.	MDB*	32 oz.
Kidney				
Monkey, rhesus	183,065	74,231	2,309	290
Monkey, cercopithecus	169,712	7,670	3,069	275
Rabbit	10,458	25,395	286	322
Guinea pig	150	---	6	---
Hamster	150	187	---	6
Dog	1,000	50	12	22
Pig	500	144	---	15
Embryo				
Chick	2,302	42,564	61	24
Mouse	570	---	--	230
Hamster	400	1,800	--	112

*MDB - Milk dilution bottles

TABLE 3

Report for the Period

January 1, 1963 - June 30, 1964

NUMBER OF CONTINUOUS CELL CULTURES ISSUED[a]

Type of Culture	Tubes	Bottles 2 oz.	Bottles MDB[b]	Bottles 32 oz.
Human				
H.Ep.#2 (PD & Co.)	5,169	102	112	1,604
KB (Eagle)	2,500	---	559	178
Hela (S-3 Eagle)	1,074	718	25	150
Human amnion (Lewis)	1,560	63	9	18
Chang's liver (Chang)	1,550	---	6	6
Human lung (Davis)	150	1,569	9	18
Animal				
BS-C-1 (Hopps)	46,409	70	12	156
Lilly monkey kidney (Hull)	15,197	544	40	527
Rabbit kidney - 13 (Beale)	17,500	300	--	---
Rabbit kidney[c]	4,419	50	--	---
Monkey stable (Tytel)	1,785	150	6	113
MA-104 (MBA)	3,300	---	--	---
Monkey heart (Salk)	60	116	--	---

(a) 5,415 32 oz. culture stock bottles were prepared
(b) MDB - Milk dilution bottles
(c) Second generation cells

Laboratory Chief's Summary
Virology and Rickettsiology
January 1, 1963 through June 1964

Administrative Aspects. In December 1963, Dr. Alexis Shelokov was appointed Chief of the Laboratory to fill the vacancy resulting from Dr. Joseph E. Smadel's death in July 1963.

Preliminary functional changes in line with the planned reorganization have taken place: the Section on General Virology is being transferred to Laboratory of Viral Immunology, while the Tissue Culture Section of LVI is being transferred to this Laboratory. A redefinition of the other Sections within LVR is also planned.

The Pakistan project and Mrs. Doris Parkinson, Special Assistant for this project, were transferred to the Office of International Research in November 1963.

Dr. S. Martin Harwin joined DBS in July 1963. Dr. Nicola M. Tauraso transferred to DBS with Dr. Shelokov from the Laboratory of Tropical Virology of NIAID. Dr. Mahmet Saglam, a Turkish Army Officer from Ankara, Turkey has been with the Section on Respiratory Viruses since February 1, 1963.

Miss Elizabeth Jackson of the Section on Basic Virology and Rickettsiology resigned in March 1964 to join the staff of the University of Maryland School of Medicine. Dr. Motoichi Hatano and Dr. Seiya Kohno completed their professional visits with the Division and returned to Japan in December 1963 and January 1964, respectively.

Rickettsiae. Rickettsial studies were continued during this reporting period. A most exciting finding was that microorganisms other than viruses can induce interferon production. A rickettsial interferon was induced by R. tsutsugamushi; it will be important to determine if other rickettsiae induce interferon and what role interferon plays in rickettsial infections in vivo.

Other projects concerned the development of a stable and potent killed epidemic typhus vaccine and a reevaluation of the present immunization schedule. The typhus rickettsiae in the infectious egg material were fractionated and the antigenicity and immunogenicity of these fractions were examined in an attempt to prepare purified antigens.

Influenza. With but a few other groups in this country, this laboratory continues to be concerned with the pathogenesis and immunogenesis of influenza: carefully designed human volunteer studies to elucidate these problems are in progress in collaboration with Laboratory of Clinical Investigations, NIAID.

A better system for the determination of the CCA content of influenza virus vaccines is under development in cooperation with the Auto Analyzer instrument of the Technicon Company.

A simple cell culture plaque assay method for influenza virus was developed; inhibitor-resistant and inhibitor-sensitive particles of the A2/305 prototype virus may differ in their antigenicity, a finding of possible future importance in the development of more potent vaccines.

Adenovirus Vaccines. Studies on the variables in the potency assay of formalin-inactivated trivalent adenovirus vaccines, defined the parameters of (1) number of immunizing injections, (2) response of monotypic component and the combination of these and (3) virus inhibitors in the sera of test animals before immunization.

Antibodies Against Simian Viruses in Human Sera. The prevalence of virus neutralizing substances against monkey adenovirus SV_{20} and myxovirus SV_5 was determined in sera from 102 infants, children and adults living in two markedly different sociologic and ecologic settings (New Guinea and the United States). The results suggest the possibility that SV_5 and SV_{20}, or agents antigenically related to them, might be infectious for man.

Human Hepatitis Viruses. The general properties of the A-1 virus were previously reported. A significant development was the demonstration of neutralizing antibody changes in the sera from documented cases of hepatitis; of particular interest were seven individuals from New Jersey who developed hepatitis with jaundice and from whom two or more specimens were available; 6 of these individuals showed four-fold or greater antibody changes over a period of 3 to 6 months implying an etiological relationship between these cases and A-1 virus.

Antimicrobial Agents in Foodstuffs. Preliminary characterization of these substances has been completed. Five different antiviral and antibacterial paolins have so far been isolated from abalone, oyster and other shellfish. The first three are probably complex proteins, the fourth is most likely a histone and the fifth - a complex lipid. Their possible usefulness as an antimicrobial means of treatment and prevention of certain infections in experimental animals is being evaluated. In collaboration with the Laboratory of Infectious Diseases, NIAID, a study is underway to determine whether commerical clam juice fed daily to a nursery population will affect the incidence of bacterial and viral upper respiratory infections.

Avian Leukosis Viruses in Relation to Human Vaccines. The Rubin RIF test has been in use at DBS for detecting the avian leukosis viruses in the vaccines of chick embryo origin. Because the procedure is cumbersone and time consuming, several other techniques have been explored so far without success. It is planned to evaluate next the COFAL procedure, developed at NIAID, as a supplement or as an eventual replacement for the RIF test.

Arboviruses. Vaccines against certain arboviruses of public health importance may soon come within the purview of the Division. A small laboratory has been now established at DBS to provide the technical competency in arbovirus animal work, tissue culture and serology, to establish a reference collection of arthropod-borne viruses for the immediate and future needs of the Division and to utilize these resources in research on selected arboviruses, including those of importance as vaccine candidates.

Preparation of Cell Cultures for Research and Vaccine Test Use. A total of 468,980 tubes, 155,723 oz. bottles, 6,261 milk dilution bottles and 4,066 32 oz. bottles of standard and experimental primary and serial cell cultures for research and testing of viral vaccines were prepared during this period. These cultures provide an indispensable tool for the fulfillment of the vaccine testing responsibility of the Division and for the use by research investigators in this and other laboratories of DBS and even certain other Institutes.

Safety Testing of Killed Virus Vaccines in Cell Culture. Upon determining the viral susceptibility of the several cell systems, the cultures were used for safety testing of the killed virus vaccines. During the calendar year 1963 samples of 11 lots of inactivated poliovirus vaccine, 8 lots of adenovirus vaccine and 16 lots of measles vaccines were tested. This project fulfills a statutory responsibility of the Division.

Serial No. DBS 53
1. Virology & Rickettsiology
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Administration, research planning and coordination

Principal Investigator: Dr. Alexis Shelokov

Other Investigators: None

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1 3/4
Professional: 1/4
Other: 1 1/2

Project Description:

The project, for the purposes of this report, was initiated on 1 December 1963 to furnish supervisory and administrative services to all research projects and biologics control activities in the Laboratory as follows: (a) over-all planning of research and control functions and their coordination among and within the several Sections of the Laboratory, (b) supervision over personnel, maintenance, travel and correspondence, (c) requisitioning and supervision of equipment and supplies, (d) reviewing, editing and revising scientific and technical reports and manuscripts, (e) preparation of administrative reports, exhibits and other publication materials, (f) official liaison and communications with the manufacturers of viral vaccines and other biologics, (g) consultation services to individuals, academic institutions and government agencies, including liaison activities with other branches of the Service, foreign governments and international agencies, (h) maintenance of reference library and reprint files.

Part B included Yes/X/No/___/

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Craighead, J. E., Peralta, P. H., Murnane, T. G. and Shelokov, A.: Oral infection of swine with the encephalomyocarditis virus. J. Infect. Dis. 112:205-212, 1963.

Shelokov, A.: Comparative epizootiology of animal viruses in Tropical America. Proceedings, First Int. Conf. on Wildlife Dis., High View, New York, June 24-27, 1962, Wildlife Dis. Assoc. pp. 278-281, 1963.

Craighead, J. E., Peralta, P. H. and Shelokov, A.: Demonstration of encephalomyocarditis virus antibody in human serums from Panama. Proc. Soc. Exp. Biol. & Med. 114: 500-503, 1963.

Wiebenga, N. H., Shelokov, A., Gibbs, J. C.,Jr., and Mackenzie, R. B.: Epidemic hemorrhagic fever in Bolivia. II. Demonstration of complement fixing antibody in patients' sera with Junin virus antigen. Am. J. Trop. Med. & Hyg. (In press, July 1964).

Craighead, J. E., Shelokov, A. and Brody, J. A.: Enterovirus infections of Panamanian children. An outbreak of poliomyelitis during a 12 month population survey. Am. J. Hyg. (In press, May 1964).

Honors - Dr. Shelokov

1. Awarded diploma in Medical Virology by the American Board of Microbiology

2. Re-elected member of Scientific Advisory Board, Gorgas Memorial Institute, Washington, D. C. and Panama, R. de P.

Serial No. DBS 54
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on arthropod-borne viruses (arboviruses)

Principal Investigator: Dr. Alexis Shelokov

Other Investigators: Dr. Nicola M. Tauraso
Inta Ziedins

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1 1/4
Professional: 1/4
Other: 1

Project Description:

Objectives: 1. To establish an arbovirus facility with competency in the techniques of animal work, tissue culture and serology for the study of the arthropod-borne viruses. 2. To establish a reference collection of arboviruses for the immediate and future needs of the Division. 3. To utilize these resources in research on selected arboviruses, including those of importance as vaccine candidates.

Methods Employed: Many strains of arboviruses are being collected from various reliable sources. Employing basic techniques of both animal work and tissue culture, pools of the above viruses and serological facilities will include complement-fixation, hemagglutination, hemagglutination-inhibition and neutralization tests, all basic to the study of arboviruses.

Major Findings: The Arbovirus Unit was established in January 1964. In the short time since, a number of arboviruses have been collected. Large working pools of viruses needed in the execution of DBS Project No. 54 have been prepared. Work is underway utilizing both animal and tissue culture facilities.

Significance to Bio-medical Research and the Program of the Division: Many of the continental states, as well as Hawaii, Alaska and Puerto Rico, possess the ecological prerequisites of potential vectors and reservoirs necessary for initiation of arbovirus epidemics. This has, in fact, happened in the recent U. S. outbreaks of dengue, St. Louis encephalitis, eastern and western equine encephalitis. Vaccines against these and other arboviruses of importance to the world- and the U. S. personnel and travelers abroad- are being developed. Some may soon come within the purview of the Division of Biologic Standards.

Proposed Course of the Project: The studies will continue as outlined.

Part B included Yes/ / No/X /

Serial No. DBS 55
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Biologic properties of the sandfly viruses

Principal Investigator: Dr. Alexis Shelokov

Other Investigators: Dr. Nicola M. Tauraso
Inta Ziedins

Cooperating Units: Middle America Research Unit
Rockefeller Foundation Virus Laboratories
University of Maryland, School of Medicine

Man Years (computed for the 18 month period)
Total: 3/4
Professional: 1/2
Other: 1/4

Project Description:

Objectives: To develop the necessary techniques and to examine the properties of the several viruses which in some way share the common ecologic denominator of the phlebotomus sandfly.

Methods Employed: Viruses are propagated in cell culture and susceptible animals and studied by standard and experimental immunological procedures.

Major Findings: This is a new project. The necessary virus pools, antigens and antibody reagents are being prepared. The following viruses are under study: the prototype strains and the recent Pakistan isolates of Naples and Sicilian sandfly fever viruses, Chagres and Icoaraci viruses recently isolated from a human in Panama and from a Brazilian mammal, respectively (both related to the Naples virus); Changuinola and the related Irituia viruses isolated from the Panamanian phlebotomus and a Brazilian mammal, respectively; vesicular stomatitis virus - Indiana type, isolated from Panamanian phlebotomus, and vesicular stomatitis virus - New Jersey type, never isolated from any but the mammalian source.

Significance to Bio-medical Research and Program of the Division: It is important to define the public health significance of the newly discovered viruses found to be related to sandfly fever, a disease of epidemic importance.

Proposed Course of the Project: The work has just begun.

Part B included Yes/ / No/X/

Serial No. DBS 56
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on virulence and avirulence in rickettsiae

Principal Investigator: Hope E. Hopps

Other Investigators: Dr. Lewellys F. Barker

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1 3/4
Professional: 3/4
Other: 1

Project Description:

Objectives: The overall objective of this project is to study the characteristics of avirulent and virulent rickettsiae from the typhus, spotted fever, and scrub typhus groups. Current studies are concerned with the behavior in tissue cultures of the virulent Breinl and the avirulent E strains of epidemic typhus (Rickettsia prowazeki).

Methods Employed: Modern tissue culture and embryonated egg techniques and the standard serologic procedures used in studies on viral and rickettsial agents were employed.

Major Findings: Both the virulent Breinl and the avirulent E strains grew in healthy, multiplying BS-C-1 monkey kidney cell cultures; however, the virulent strain appeared to multiply more rapidly. Preliminary data indicate that this difference in growth rate of the organisms can be markedly enhanced by maintaining the host BS-C-1 cells in a non-multiplying state, i.e., at maximum population levels.

Significance to Bio-medical Research and Program of the Division: Increased interest in the use of attenuated rickettsial vaccines makes necessary a better understanding of those factors which influence virulence and avirulence.

Proposed Course of the Project: This is a continuing project. Further studies will be carried out in tissue cultures using various mammalian cell types and growth conditions in an attempt to find virulence and avirulence markers.

Part B included Yes / / No /X/

Serial No. DBS 57
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on a possible psittacosis-like agent isolated from Cercopithecus aethiops tissue culture material

Principal Investigator: Hope E. Hopps

Other Investigators: Barbara C. Bernheim
Dr. Lewellys F. Barker

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1
Professional: 1/2
Other: 1/2

Project Description:

Objectives: The primary objective of the project is the biological characterization of the agent and the determination of its prevalence in terms of specific antibody in human and simian sera.

Methods Employed: Modern tissue culture and embryonated egg techniques and the standard serologic procedures used in studies on viral and rickettsial agents were employed.

Major Findings: As reported previously, this agent, isolated from primary cercopithecus kidney cell cultures has many of the characteristics of a large virus or rickettsia. However, complement fixation tests with several rickettsial agents (Q fever, epidemic typhus and Rocky Mountain spotted fever) were negative. While preliminary serologic tests indicated that the isolate might be a member of the psittacosis-lymphogranuloma group, this finding could not be confirmed. The organism is not pathogenic for guinea pigs, rabbits and mice (suckling or adult). Seven of 49 human sera tested for complement fixing antibody against the agent were positive at a 1:4 dilution, but not at 1:8.

Significance to Bio-medical Research and the Program of the Division: The characterization of new agents isolated from primate tissue cultures is of importance since these tissues serve as a source for virus vaccines.

Proposed Course of the Project: This is a continuing project; as time permits, further studies on characterization of this agent will be carried out.

Part B included Yes/ / No /X/

Serial No. DBS 58
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Biologic studies on resistance inducing factor (RIF) in tissue cultures

Principal Investigator: Dr. Seiya Kohno (Visiting Associate)

Other Investigators: Dr. C. J. Gibbs (NINDB)
William G. Jahnes

Cooperating Units: Collaborative Field Research Unit (NINDB)

Man Years(computed for the 18 month period)
Total: 1 1/2
Professional: 1 1/2
Other: 0

Project Description:

Objectives: The primary objective of the project is to find a less cumbersome and time consuming procedure by which the presence of resistance-inducing factor (RIF), a member of the avian leukosis complex, can be detected in vaccines of avian origin.

Methods Employed: Standard tissue culture and serologic techniques were employed.

Major Findings: (1) Hemagglutination and hemadsorption. A tissue culture antigen prepared from RIF-infected primary chick embryo tissue was tested for its hemagglutinating capacity in a microtiter test using a variety of red blood cells (goose, 2-day old mouse, adult mouse, 1-day old hamster, adult guinea pig, rhesus monkey and human O, at various temperatures (4°, 20° and 37°C) and pH levels (5.4 to 7.4 in 0.2 increments). Although some partial hemagglutination was observed at low dilutions of antigen, its specificity to RIF was questionable and the results were considered as negative. Moreover, when RIF-infected tissue cultures were examined for their ability to hemadsorb, using the same systems as outlined for the hemagglutination tests, no hemadsorption was noted. (2) Detection of RIF by differences in behavior of infected cells. Two parameters of biologic activity were used: cell multiplication and enzymatic activity; for the latter test system, breakdown of adenosine triphosphate (ATP) was chosen. No

significant reproducible differences were observed when RIF-infected and control cultures were examined. (3) Establishment of a complement fixation assay procedure. Attempts to produce suitable antisera in hamsters against Rous sarcoma virus, (RSV) a RIF-related agent are in progress. It has been possible to produce tumors in hamsters upon inoculation with RSV. Sera from these animals will be tested for its reactivity with RIF antigen prepared from infected chick embryo tissue cultures. (4) Attempts to use other cell lines for RIF detection. Thus far, only one cell line has been tested, viz., BS-C-1. No CPE was observed in infected cultures nor was there any evidence of RIF build-up as determined by interference studies with infected BS-C-1 cells which were held for 7 passages and then challenged with vesicular stomatitis virus (VSV). (5) Attempts to establish a plaque assay system. Both Sindbis virus and VSV were tested in an attempt to establish a plaque assay system which might be substituted for Rous sarcoma virus as the challenge agent in the current RIF assay system. No interference with Sindbis virus by RIF could be detected in 4 separate experiments. With VSV, interference was measured in only one of 5 experiments. (6) Interferon production. When primary chick embryo tissue cultures were treated with either tissue culture medium or the tissue culture fluid from cultures infected with RIF and then challenged with Sindbis virus, no difference occurred in the number of plaques formed in the treated and control cultures. Thus, under the conditions employed in this Laboratory, RIF agent does not induce interferon formation.

Significance to Bio-medical Research and the Program of the Division. The avian leukosis group of agents, of which Rous sarcoma (RSV) and resistance inducing factor (RIF) are members, constitute a major problem in terms of vaccine production. More sensitive and less cumbersome methods must be devised for detecting the presence of these agents in vaccines of chick tissue origin.

Proposed Course of the Project: Particular emphasis will be placed on establishing a workable complement fixation procedure. Further, studies concerning the possible use of agents other than Rous in the present RIF assay system will be continued.

Part B included Yes/ / No/X /

Serial No. DBS 59
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Development of continuous tissue culture lines for use in testing of vaccines

Principal Investigator: Hope E. Hopps

Other Investigators: Barbara C. Bernheim

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 2 1/4
Professional: 1 1/4
Other: 1

Project Description:

Objectives: To establish cell lines or devise tissue culture systems suitable for laboratory testing of vaccines.

Methods Employed: Modern tissue culture techniques and the standard procedures in tissue culture research were employed.

Major Findings: During the past year, studies with tissue culture cell lines have concerned the following: (A) BS-C-1 cercopithecus kidney: Experimental work with this line is essentially completed and studies describing its characterization appeared in the J. Immunol., October, 1963. The line will continue to be maintained in this Laboratory since numerous requests for it are being received. Studies are under way to establish a second stable cercopithecus kidney cell line. (B) Chick embryo cell line: The main objective of the project is to establish a cell line from chick embryo tissue which might be suitable for use in assaying for RIF, a virus of the fowl leukosis complex, in live measles vaccines; as yet, a continuous line has not been established. This project will be continued on a part time basis, i.e., when new approaches are devised.(C) Rabbit kidney cell line (RK 13): This cell line was established by Dr. A. J. Beale of the Glaxo Laboratories, England, and is of particular interest because of its sensitivity to infection with rubella virus. The line was received in this Laboratory in October, 1963; cultures are now being maintained and stocks for liquid nitrogen storage have been prepared. Since rubella induces a subtle cytopathic change in these cells which is

only visible by phase optics, attempts will be made to enhance or intensify these cytopathic changes by altering the environment of the host cell and perhaps rendering it more sensitive to rubella infection. Accomplishment of this objective would make the RK 13 cell line a more practical tool for vaccine testing. Attempts are now being made to free the line of contamination with PPLO.

Significance to Bio-medical Research and the Program of the Division: This project has provided a suitable cell system (BS-C-1) for isolation of SV40 and for measles potency testing. The development of cell lines free of adventitious agents is important to virus vaccine testing programs.

Proposed Course of the Project: (1) The BS-C-1 line will continue to be maintained in this laboratory since numerous requests for it are received. (2) Recently a line of cells reported to be stable chick embryo cells has been received; if the line can be maintained, its susceptibility to infection with RIF will be tested.

Part B included Yes /X/ No / /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards and Publications

Publications other than abstracts from this project:

Hopps, H. E., Bernheim, B. C., Nisalak, A., Tjio, J. H., Smadel, J. E., Biologic characteristics of a continuous kidney cell line derived from the African green monkey, J. Immunol., 91: 416-424, 1963.

Serial No. DBS 60
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Reports
January 1, 1963 through June 30, 1964

Part A

Project Title: General aspects of virology and rickettsiology

Principal Investigator: Dr. Joseph E. Smadel

Other Investigators: Elizabeth B. Jackson
Dr. William McD. Hammon

Cooperating Unit: None

Man Years (computed for the 18 month period)
Total: 1/4
Professional: 1/4
Other: 0

Project Description:

Objectives: This particular project is included among those of the Laboratory of Virology and Rickettsiology in order to provide a mechanism for reporting work which does not clearly fall within the purview of other project reports. One of the most important duties of this Laboratory is to keep abreast of advances in the expanding field of virology, especially as they relate to the development of new vaccines. One way of doing this is by attendance at, and participation in, various conferences and symposia. The report lists several publications in the general field of immunology, virology and rickettsiology.

Major Findings: Principal investigator, in collaboration with Dr. William McD. Hammon of the University of Pittsburgh School of Public Health, organized a Seminar on Hemorrhagic Fevers held during the meeting of the Seventh International Congresses on Tropical Medicine and Malaria at Rio de Janeiro, Brazil, in September, 1963. Titles and authors of the papers follow:

1. Epidemic Hemorrhagic Fever with Renal Syndrome in Europe - Prof. M. P. Chumakov, USSR

2. Hemorrhagic Fevers of Southeast Asia - Dr. S. B. Halstead and Dr. C. Yamarat, Thailand

3. Hemorrhagic Fevers in South America: (1) Argentina - Dr. I. M. Pintos, Buenos Aires; (2) Bolivia - Dr. R. B. MacKenzie (MARU), Canal Zone

4. Crimean Hemorrhagic Fever in Middle Asia - Dr. M. K. Voroshilova, USSR

5. Kyasanur Forest Disease - Dr. T. R. Rao and Dr. J. M. Boshell, India

The papers were discussed by scientists working on these and related diseases. The etiology of these various diseases is mixed; thus, the problems of preparing vaccines against them are manifold.

Significance to Bio-medical Research and the Program of the Division: See under "Objectives."

Proposed Course of the Project: The value of this reporting device is being reviewed.

Part B included Yes/ X/ No/ /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Smadel, J. E.: Smallpox. In McDermott, W., and Beeson, P. B. (eds.): Cecil-Loeb Textbook of Medicine (ed. 11) Philadelphia W. B. Saunders Co., 1963, pp. 40-45.

Smadel, J. E.: Vaccinia. Ibid, pp. 45-48.

Smadel, J. E.: Rocky Mountain spotted fever. Ibid, pp. 130-136.

Smadel, J. E.: Tick-borne rickettsioses of the Eastern Hemisphere. Ibid, pp. 136-138.

Smadel, J. E.: Rickettsialpox. Ibid, pp. 138-140.

Smadel, J.E.: Scrub typhus. Ibid, pp. 140-143.

Smadel, J. E.: Symposium on immunization against arbovirus infections. Introduction and summary. Am. J. Trop. Med. 12: 586-639, 1963.

Woodward, T. E. and Smadel, J. E.: Management of typhoid fever and its complications. In Science, Technology & Development. Vol. VI., Health and Nutrition, Washington, Government Printing Office, 1963, pp. 94-110.

Woodward, T. E. and Smadel, J. E.: Management of typhoid fever and its complications. Ann. Int. Med. 60: 144-157, 1964.

Serial No. DBS 61
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Mechanisms of intracellular infection

Principal Investigator: Hope E. Hopps

Other Investigators: Dr. Seiya Kohno (Visiting Associate)
Elizabeth B. Jackson
Barbara C. Bernheim
Dr. Joseph E. Smadel

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 1 1/2
Professional: 1
Other: 1/2

Project Description:

Objectives: The main objective of this long-continuing project is the accumulation of information concerning the mammalian host cell and its response to microbial infection with particular emphasis on the carrier state and the means by which infected cells are freed of their parasites.

Methods Employed: Modern tissue culture techniques and the standard procedures used in a research laboratory engaged in studies on viral and rickettsial agents were employed.

Major Findings: When primary chick embryo monolayers (PCE) were infected with the Karp strain of R. tsutsugamushi a substance inhibitory to virus multiplication was detected in the surrounding tissue culture fluid. Production of the inhibitory material paralleled rickettsial multiplication and none was found when growth of the rickettsiae was inhibited by addition of chloramphenicol (5 ug/ml) 2 hrs after infection; chloramphenicol exerted no such effect on production of viral interferon under the same experimental conditions. Incubation of the inhibitor with PCE followed by infection with Sindbis, vesicular stomatitis or influenza PR8 viruses resulted in marked inter-

ference with virus multiplication as measured by reduction in plaque formation or hemagglutinin titer. Characterization of "rickettsial interferon" revealed that it possessed many of the physical and biological properties ascribed to viral interferon: (1) a high degree of tissue specificity was demonstrated; no inhibition of virus multiplication occurred when PCE-produced interferon was assayed in other tissue culture systems including mouse embryo, hamster kidney, BS-C-1 and primary cercopithecus kidney; (2) in vitro incubation of inhibitor and virus at 35°C for 1 hr did not result in loss of viral infectivity; (3) interferon activity was destroyed when the material was treated with trypsin or heated to 80°C for 1 hr but remained stable after heating at 60°C for 1 hr or after holding at pH 2.5 for 3 hrs at 4°C. The data indicate that interferon production is not limited to virus or nucleic acid-host cell interaction but may occur with more complex microbial forms.

Significance to Bio-medical Research and the Program of the Division: The finding that microorganisms other than viruses can induce interferon production is of basic importance to our understanding of the interferon phenomenon.

Proposed Course of the Project: This is a continuing project and experiments will be undertaken: (a) to determine what role interferon plays in rickettsial infections in vivo and (b) to determine whether other rickettsiae induce interferon production.

Part B included Yes/ X /No/ /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Smadel, J. E., Intracellular infection and the carrier state, Science, 140: 153-160, 1963. (Written from a National Institutes of Health Lecture, 12 December 1962).

Smadel, J. E.: Intracellular infections. Bull. N. Y. Acad. Med. 39: 156-172, 1963.

Serial No. DBS 62
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Antigenic studies of epidemic typhus rickettsiae

Principal Investigator: Dr. Lewellys F. Barker

Other Investigator: Judith K. Patt

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 2
Professional: 1/2
Other: 1 1/2

Project Description:

Objectives: The objective is to investigate the antigenicity and the immunogenicity of three fractions of epidemic typhus rickettsiae. These fractions are the soluble antigen, the cell wall and the intracellular material.

Methods Employed: Rickettsiae are purified from infected yolk sacs by differential centrifugation, treatment with celite, albumin and trypsin and sucrose gradient centrifugation. Disruption of the organisms, separating the cell walls from the intracellular material, is done with a Mickle apparatus. The cell walls are then separated from intact rickettsiae by sucrose gradient centrifugation. After purification, the cell walls and intact rickettsiae are examined with the electron microscope. The soluble antigen is obtained by ether extraction of infected yolk sac suspensions. Standard techniques are then employed to determine the antigenic and immunogenic properties of the materials.

Major Findings: Preliminary results have shown a high degree of antigenic activity in all three fractions studied. In the complement fixation test 10-20 micrograms are necessary for a positive reaction to take place. In the mouse protection test, a fraction of a microgram protects mice against challenge with two units of toxin. No information is available as yet on which fractions will protect guinea pigs against a challenge with infectious material.

Significance to Bio-medical Research and the Program of the Division: Commercial epidemic typhus vaccine is a crude product containing a large quantity of egg material as well as intact and partially degraded rickettsiae. As a vaccine ideally should contain only the antigen(s) needed to evoke protective immunity, it is important to look for these antigens in complex microorganisms such as rickettsiae.

Proposed Course of the Project: This is a continuing project which will focus for the time being on the three major fractions mentioned under Objectives. These fractions will be characterized by physical, chemical and immunologic means. It is planned to study their antigenic properties in the complement fixation test and in intact animals, which will be challenged with rickettsial toxin and infection. Further fractionation of these materials will be attempted depending on the results obtained.

Part B included Yes/ /No/ X /

Serial No. DBS 63
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies of killed epidemic typhus vaccine

Principal Investigator: Dr. Lewellys F. Barker

Other Investigators: Judith K. Patt
Elizabeth B. Jackson
Dr. Joseph E. Smadel

Cooperating Units: Naval Medical Field Research Laboratory
Camp Lejeune, North Carolina

Man Years (computed for the 18 month period)
Total: 2
Professional: 1/2
Other: 1 1/2

Project Description:

Objectives: This study was designed to determine (1) the dose-response curve to a primary injection of licensed commercial epidemic typhus vaccine, and (2) the amount of vaccine required in the primary dose to prepare individuals for a booster response at a later date.

Methods Employed: The vaccinees were Marine recruits at Camp Lejeune, N. C. The vaccine was administered by jet gun. The doses in the primary injections were as follows: Group A - 0.5 ml of undiluted vaccine, Group B - 1.0 ml of vaccine diluted 1:16, Group C - 0.5 ml of vaccine diluted 1:16, Group D - 1.0 ml of vaccine diluted 1:64, Group E - 1.0 ml of vaccine diluted 1:256, Group F - 1.0 ml of vaccine diluted 1:1024, Group G - 1.0 ml of saline (control group). The booster dose given to all individuals in the study was 0.5 ml of vaccine diluted 1:16. Serum samples were collected at appropriate times and shipped to DBS. Complement-fixation and mouse toxin-neutralization tests were performed according to standard techniques.

Major Findings: The first objective was accomplished in 1961 and has been reported; the studies covered in this report concern the second objective. (1) Men in Group B showed evidence of sensitization, so that the percent of the group which responded to the booster injection was significantly greater than in the control group. (2) Groups C, D, E, and F, which were primed with smaller doses of antigen, showed

consistently but not significantly higher percent responses to the booster than the control group. (3) The promptness and height of the booster response appear to be related more to the size of the booster dose than to the size of the sensitizing dose. Also important in obtaining a good booster response is the time interval between the primary and the booster dose. The required interval appeared to be directly related to the size of the primary dose. Group A showed no response to the booster, presumably because of the high degree of residual immunity present.

Significance to Bio-medical Research and the Program of the Division: This study was designed to reassess the necessary dose of commercial typhus vaccine for adequate immunization. Also in the event that it should be desirable to incorporate typhus vaccine into a polyvalent vaccine it would be useful to know the minimum dose of this antigen that will produce the desired effect. This was another reason for the titration of the primary or sensitizing dose of typhus vaccine.

Proposed Course of the Project: This is a continuing project. No further vaccination groups are planned at present. Studies have been initiated to determine the physical-chemical characteristics of the antibodies involved in the primary and booster response. Studies are planned to evaluate the assay techniques for measuring epidemic typhus vaccine potency.

Part B included Yes/ / No/X /

Serial No. DBS 64
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Rickettsial vaccines

Principal Investigator: Elizabeth B. Jackson

Other Investigators: Dr. Joseph E. Smadel
Cdr. Henry H. Bloom
Cdr. Benjamin F. Gundelfinger
Dr. Richard A. Ormsbee
Lt. Col. Stefano Vivona
Dr. Joseph Lowenthal
Dr. Sanford Berman

Cooperating Units: Naval Medical Field Research Laboratory
Camp Lejeune, North Carolina
Rocky Mountain Laboratory, NIAID
Division of Communicable Diseases, WRAIR

Man Years: (computed for the 18 month period)
Total: 1/2
Professional: 1/2
Other: 0

Project Description:

Objectives: I. Improvement of established rickettsial vaccines. II. Development of new rickettsial vaccines.

Methods Employed: Standard procedures used in a research laboratory engaged in studies on rickettsial vaccines.

Major Findings: Typhus vaccine, living, attenuated Strain E. This study was undertaken (1) to develop procedures for the production and lyophilization of a stable, living, attenuated epidemic typhus, Strain E, vaccine of high titer and (2) to develop an acceptable, reliable infectivity assay to serve in biologics control. The main objectives have been achieved and reported in detail in the annual reports for 1961 and 1962. A pilot lot of freeze-dried vaccine prepared in April, 1962, by procedures developed in this study has been tested for stability at various temperatures. No loss in titer was detected in material stored at -20°C for 62 weeks.

Lyophilized material rehydrated to the equivalent of a 10% yolk sac suspension and held at 5°C for 72 hrs lost only one log in titer (zero time titer = $10^{-6.6}$ ELD_{50}, 72 hour titer = $10^{-5.4}$ ELD_{50}). Hence, it appears that in the field it would be feasible to use rehydrated material for a period of at least 3 days if it were kept at 5°C.

Q fever vaccine, killed

The collaborative field study using a pilot lot of formalin-inactivated Q fever vaccine Henzerling Phase II, has been completed (see 1962 report). A manuscript prepared by members of the Division of Biologics Research, WRAIR, analyzing the results of the study is in press.

A Henzerling Phase I, inactivated Q fever vaccine has been prepared through the collaborative efforts of the Rocky Mountain Laboratory, NIAID, the Department of Biologics Research, WRAIR, and the Laboratory of Virology & Rickettsiology, DBS. Evaluation of the relative protective capacity of Phase I and Phase II vaccines in both animals and man is planned.

Regulations for the manufacture of Q fever vaccine have been developed by LVR and are available in draft form to persons interested in production of such a vaccine.

Typhus vaccine, killed, epidemic. See separate DBS report.

Significance to Bio-medical Research and the Program of the Division: Rickettsial diseases are of continuing concern to the military services and might well become of importance throughout the world following devastations such as might be brought about by nuclear attack. It is therefore important that steps be taken to produce and stockpile stable and potent rickettsial vaccines. It is also important to review immunization procedures from time to time to ensure that an adequate but not excessive antigenic mass is being administered and to consider the feasibility of a polyvalent vaccine.

Proposed Course of the Project: Indicated in main discussion of each topic.

Part B included Yes/X /No/ /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Jackson, E. B. Studies on epidemic typhus vaccines. J. Wash. Acad. Sci. 53: 179-182, 1963.

Serial No. DBS 65
1. Virology & Rickettsiology
2. Basic Virology & Rickettsiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Avian leukosis viruses in relation to human vaccines

Principal Investigator: William G. Jahnes

Other Investigators: William P. Jones

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 3
Professional: 1 1/2
Other: 1 1/2

Project Description:

Objectives: (1) To test live or inactivated viral vaccines prepared from chick embryo cells in tissue culture or from chick embryo tissue for the presence of Resistance-Inducing-Factor (RIF) (2) to develop new and more sensitive procedures for detecting the presence of viruses of the avian leukosis complex.

Methods Employed: Standard tissue culture techniques and modifications.

Major Findings: During the 18 months reporting period RIF tests for the detection of avian leukosis viruses on live and inactivated vaccines were performed as follows:

Live Vaccines	No. tested	RIF neg.	RIF pos.
Measles vaccines	46	46	0
Yellow fever vaccines	5	0	5
Yellow fever secondary seed virus(AB1017)	4	0	4
Smallpox vaccines (egg)	2	1	1
Typhus vaccine, Strain "E" (Lot CRD-1)	3	0	3

Inactivated Vaccines	No. tested	RIF neg.	RIF pos.
Parainfluenza (exptl.) vaccines	2	2	0
Type 1	2	2	0
Type 2	2	2	0
Type 3	6	6	0
Influenza vaccines	5	5	0
Epidemic typhus vaccines			
"Q" fever (exptl.) vaccines (1 dried vaccine & 1 liquid vaccine)	2	2	0
Total = 79			

Miscellaneous tests ---------- 75
Eggs, ultracentrifugation samples and experimental vaccines from various investigators

Neutralization tests were run on sera from individuals inoculated with live and killed vaccines of chick embryo tissue or chick embryo cell culture origin. Tests were also run on DBS RIF-free flock of chickens and on a RSV-free flock of chickens maintained by Dr. F. Bang, Johns Hopkins University, Baltimore, Maryland.

	No. tested	No. neg.	No. pos.
Laboratory personnel after multiple vaccinations	7	7	0
Children in Upper Volta Study #1, 20 paired sera	20	20	0
DBS RIF-free flock	20	20	0
JH RSV-free flock	10	10	0

Cooperative studies with Dr. P. Sarma, NIAID, NIH, were done utilizing a chicken enterovirus as an indicator in place of RSV in RIF assay tests. Results indicated the virus was not as efficient as RSV. Passage materials from RIF tests were tested by Dr. Sarma by the COFAL (complement-fixation for avian leukosis) test; his results will be published soon.

During the reporting period fifteen representatives of vaccine manufacturers, government agencies, and other individuals visited this Unit for the purpose of discussing techniques involved in running the RIF test. A visit was made by the senior investigator to one vaccine manufacturer.

Significance to Bio-medical Research and the Program of the Division: The RIF test is at present the procedure of choice for detecting viruses of the avian leukosis complex and, hence, has an important role in safety testing of vaccines of chick embryo origin.

Proposed Course of the Project: Attempts will be made to improve the present RIF test and to find a simpler procedure for the detection of these viruses.

Part B included Yes/ /No /X /

Serial No. DBS 66
1. Virology & Rickettsiology
2. Respiratory Viruses
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies concerned with respiratory viruses

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Calvin G. Aulisio
Jack Jenkins
Dr. Roslyn Robinson
Dr. Vernon Knight
Dr. Julius Kasel
Andrew Ferrari (Autotechnicon Co.)
Dr. D. Carleton Gajdusek

Cooperating Units: Respirovirus Unit, CDC, USPHS, Atlanta, Ga.
Laboratory of Clinical Investigation, NIAID
Autotechnicon Company, Chauncey, New York
Laboratory of Child Growth & Development, NINDB

Man Years (computed for the 18 month period)
Total: 12½
Professional: 4
Other: 8½

Project Description:

A. Influenza

Objectives: Work on this project was directed toward collection of information which would be of assistance in improving effectiveness of influenza virus vaccines.

Major Findings: Antigenic relationship of 1961-63 A2 influenza to prototype A2 1957 strain. From the work reported last year it was apparent that virus strains which caused outbreaks of influenza in separated geographic areas of the world in the winter of 1961-1962 represented members of a relatively homogenous group of A2 influenza viruses which had undergone antigenic changes of varying degrees away

from the prototype A2/Japan/305/57 virus. Within months after their recovery, the difference in antigenic composition between the contemporary viruses and the prototype virus was demonstrated. Soon thereafter an experimental lot of commercially produced monovalent vaccine containing a representative strain of new A2 virus was prepared, and the experimental vaccine was found to elicit a satisfactory serologic response in man. The studies were completed in time to incorporate a contemporary strain of influenza A2 virus into the polyvalent vaccine for use in the United States during the 1963-1964 influenza season. Detailed findings were published.

Application of the Technicon Auto Analyzer to influenza virus CCA measurements. Hirst and Pickles, more than 20 years ago, pointed out that in a large number of CCA measurements carried out in duplicate, employing the same reagents in replicate tests, 90% of the pairs showed differences greater than 12%. When even slight uncontrollable variations were introduced into the test system, the absolute numerical value of the CCA titer of a given sample of vaccine showed differences in duplicate tests in excess of 50%. Accordingly, studies were undertaken during the year in an attempt to reduce the percentage of error in measuring the CCA content of influenza virus vaccines. The current studies which are being conducted in cooperation with engineers at the Technicon Company, Chauncey, New York, are concerned with automation of CCA measurements. Determinations of the effects of several variables of the test system (pH, temperature, concentration of chicken red blood cells, red cells from different chickens, duration of virus-red cell mixing) are under study.

Proposed Course of the Project: It was observed in the course of world-wide monitoring of influenza viruses during the period 1961-1963 that attacks of influenza occurred with considerable frequency in persons who, at the time they contracted their influenza infection, possessed in their blood virus neutralizing and hemagglutination-inhibiting antibodies against the infecting virus. Despite numerous efforts made since 1940 to establish the significance of these antibodies in resistance to infection in clinical influenza, definitive information on this point is still lacking. Experiments now in progress in volunteers are designed to obtain information directed towards the definition of this relationship.

Because of the rapidity with which the CCA measurements can be made under automated conditions intensive effort will continue to be made to modify and to adapt the Technicon Auto Analyzer for use in CCA determinations.

B. Adenoviruses.

Objectives: The objective of this project is the accumulation of information which will be helpful in improving the efficacy of adenovirus vaccines and, in addition, will be of assistance in understanding the biology of adenovirus infections.

Major Findings: Definition of some variables in adenovirus potency assay tests. Formalin-inactivated trivalent adenovirus vaccines conventionally are assayed for potency in antigen extinction tests employing a quantitative measurement of neutralizing antibodies in the sera of vaccinated guinea pigs. Variables inherent in this and in other assay procedures were studied, including (1) number of immunizing injections, (2) response to monotypic components and to combinations of these, and (3) virus inhibitors in the sera of test animals before immunization. When the single injection assay procedure was employed in guinea pigs, approximately 3 times the antigenic mass of monotypic type 4 and 7 vaccines were needed to elicit formation of virus neutralizing antibody than when these monotypes were incorporated into a trivalent vaccine. In contrast, incorporation of type 3 vaccine into a trivalent preparation appeared to depress its ability to elicit formation of homotypic antibody to approximately 1/3 of that obtained with monovalent type 3 vaccine. When 3 injections were made over a 2-week period, guinea pigs responded to only a fraction of the total amounts of vaccine required to elicit antibodies in guinea pigs given a single injection. Presence of adenovirus inhibitors in prevaccination rabbit serum made it difficult to interpret assay results obtained in this host; these substances were absent in the sera of test guinea pigs.

Occurrence of neutralizing substances in the blood of man directed against monkey adenoviruses and myxoviruses. With the exception of B virus and SV40, little effort has been made to determine whether or not the so-called simian adenoviruses and myxoviruses are infectious for man. The prevalence of virus neutralizing substances against monkey adenovirus SV20 and monkey myxovirus SV5 virus was determined in sera from 182 infants, children and adults living in 2 markedly different sociologic and ecologic settings: New Guinea and the United States. SV20 neutralizing substance in titers of 1:10 to 1:160 was present in New Guinea in 70% of ½- to 5 year olds; in 72% of 6- to 18 year olds and in 78% of adults. This serum substance was absent in the United States in individuals in the ½- to 5 year old age group, but was present in titers of 1:10 to 1:80 in 33% of 6- to 18 year olds and in 22% of adults. None of the New Guinea sera and only 8% of the United States sera possessed SV5 neutralizing substance. The SV5 and SV20 inhibitors were shown to be heat stable, resistant to the action of receptor destroying enzyme and to the action of trypsin and to be a component of serum globulin: these properties are consistent with those of antibodies. These data suggest the possibility that SV5 and

SV20, or agents antigenically related to them, might be infectious for man.

Relationship between adenoviruses and human hepatitis. To answer certain questions concerning a postulated relationship between human hepatitis and adenoviruses (see Schneider, H., Candidate viruses in hepatitis. An editorial. Transfusion 1963, 3: 443-444) adenovirus complement fixing antibody levels were measured in acute and convalescent bloods obtained from 50 infectious hepatitis patients. It was found in tests employing a 1:10 dilution of serum that no detectable adenovirus group CF antibody was present in 11 of the 50 serum pairs. In the remaining 39 pairs, the level of antibody present in the acute specimen of the pair did not differ from that in the convalescent specimen. It would appear, therefore, that the chances are very slight that adenoviruses were etiologically associated with the illnesses clinically diagnosed as infectious hepatitis in the 50 patients included in this study.

Proposed Course of this Project: In the course of the work concerned with definition of the variables in adenovirus vaccine potency assays, it was observed that some lots of adenovirus vaccines showed a marked depletion of potency when stored in the liquid state at 4°C for a period of a year. Accordingly, studies are now underway to determine whether or not the adenovirus vaccine containing virus types 3, 4 and 7 can be dried without appreciable decline in its antigenic potency. Studies are also in progress in an attempt to determine the significance of the presence of SV5 and SV20 antibodies in the serum of man, while continued consideration is being given to the possibility that respiratory viruses might on rare occasion produce in man illnesses clinically diagnosed as infectious hepatitis.

Part B included Yes/X / No/ /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards and Publications

Publications other than abstracts from this project:

Morris, J. A., Hatano, M., Robinson, R. Q., Aulisio, C. G., and Smadel, J. E. Antigenic relationship of 1961-1963 A2 influenza viruses to prototype A2 1957. Proc. Soc. Exp. Biol. and Med. 1963, 114: 406-413.

Aulisio, C. G. and Morris, J. A., Definition of some variables in adenovirus potency assay tests. J. Inf. Dis., in press

Serial No. DBS 67
1. Virology & Rickettsiology
2. Respiratory Viruses
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies concerned with virus identification

Principal Investigator: Dr. J. Anthony Morris

Other Investigators: Calvin G. Aulisio
Jack Jenkins
Marilyn Bozeman
Dr. William Pond
Dr. D. Carleton Gajdusek

Cooperating Units: WRAIR, Washington, D. C.
University of Miami, Miami, Florida
Laboratory of Child Growth & Development, NINDB

Man Years (computed for the 18 month period)
Total: 1
Professional: 1/2
Other: 1/2

Project Description:

A new hemadsorbing virus. As reported in the Annual Report, 1962, a hemadsorbing agent, which appears to be a new myxovirus, was recovered from the visceral tissue of a mouse. During the current year studies concerned with the determination of the physical and biologic properties of the agent were completed, the findings were published and the virus was made available for study to interested investigators in this and several other countries.

Unidentified transmissible agent. An unidentified transmissible agent was recovered from the visceral tissues of a rabbit. The new agent which appears to be a virus, was not neutralized by antisera prepared against any of a number of known small viruses, but does appear on the basis of very preliminary tests to possess certain properties characteristic of the psittacosis-lymphogranuloma venereum group of viruses. The agent grew readily in embryonated eggs, produced lethal infection following intracerebral injection into white mice, and produced degenerative changes in a variety of primary and continuous cell cultures. Neutralizing antibodies against the new agent were found in 4 of 25 rabbit sera in titers ranging from 1:10 to 1:80, but were not found in the blood of 197 animals belonging to

9 other species (including 131 sera obtained from man).

Viruses resistant to the action of chemical and physical agents. A chronic, progressive, degenerative disease of the central nervous system has been produced in mice inoculated with the scrapie agent, an agent of unusual resistance (resists exposure to temperature of boiling water for 30 minutes and to exposure to a 1:400 dilution of formalin for prolonged periods). The incidence and incubation period and the nature of the lesion associated with scrapie infection in inoculated mice have been determined, and the findings published.

Proposed Course of the Project: Investigation of the identity of transmissible agents recovered from the tissues of animals which are used in potency assays of respiratory viruses vaccines will continue and is expected to assist in the definition of factors which might be inherent variables in the assay system. Studies of viruses resistant to the action of chemical and physical agents will continue.

Part B included Yes/ X /No / /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Morris, J. A., F. M. Bozeman, C. G. Aulisio and A. Shirai, A new hemadsorbing virus. Proc. Soc. Exp. Biol. and Med. 1963, 113: 296-300.

Morris, J. A. and D. C. Gajdusek. Encephalopathy in mice following inoculation of scrapie sheep brain. Nature, 1963, 197: 1084-1086.

Serial No. DBS 68
1. Virology & Rickettsiology
2. Respiratory Viruses
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Plaque assay and characterization of inhibitor resistant and sensitive variants of influenza virus

Principal Investigator: Dr. Motoichi Hatano

Other Investigator: Dr. S. Martin Harwin

Cooperating Units: None

Man Years (computed for the 18 month period)
Total: 2 1/4
Professional: 1 1/2
Other: 3/4

Project Description:

Objectives: One objective of this project was to establish a simple plaque assay method in cell culture applicable to all strains of influenza virus. The other objective was to isolate influenza virus variants differing in biological properties. These contrasting properties will act as markers for the study of influenza virus genetics.

Methods Employed: Modern tissue culture techniques in the standard procedures used in a research laboratory engaged in studies on viral agents were employed.

Major Findings: All of a variety of prototype and epidemic influenza strains tested could be efficiently plaque assayed in rhesus and cercopithecus monkey kidney cell cultures using a standard incubator without CO_2. Influenza virus variants of A2/305 and A2/170 were found to differ in a number of properties sensitivity to normal serum inhibitors and trypsin, antigenicity, plaque size, interference, and agglutination of erythrocytes treated with receptor destroying enzyme. These variants did not significantly differ in the pattern of elution from erythrocytes, adsorption, growth and ultraviolet inactivation rates. Resistant particles of A2/305 and A2/170 differed in some biological properties.

Significance to Bio-medical Research and the Program of the Division: The heterogenicity of particles of varying proportion in Asian influenza virus stocks and the demonstration that A2/305 inhibitor resistant and sensitive particles differ in antigenicity may be a consideration in future influenza vaccine studies and serological diagnoses. Successful prophylaxis may depend upon vaccination with an optimal proportion of inhibitor resistant and sensitive particles.

Influenza virus genetics can be performed with pure clone virus using the developed plaque method. Studies using viruses with RNA as genetic material may lead to mapping of genetic determinants on the RNA.

Proposed Course of the Project: This project is now completed and the findings are being prepared for publication.

Part B included Yes/ / No/X/

Serial No. DBS 69
1. Virology & Rickettsiology
2. General Virology
3. Bethesda 14, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Investigations concerned with human hepatitis viruses

Principal Investigator: Dr. Joseph P. O'Malley

Other Investigators: Dr. Ruth Kirschstein, LVI
John Thiel, LBB

Cooperating Units: Laboratory of Pathology, DBS
Laboratory of Biophysics & Biochemistry, DBS

Man Years (computed for the 18 month period)
Total: 4 1/6
Professional: 2 1/6
Other: 2

Project Description:

Objectives: The purpose of this project is (1) to develop suitable laboratory methods for cultivating and handling one or more of the human hepatitis viruses, and (2) to evaluate the importance to man of certain viruses presumed to cause human hepatitis.

Methods Employed: The tissue culture methods of a virus research laboratory are employed in this work. In studies on A-1 virus, particular use is made of a viral plaque counting technique with chick embryo monolayers serving as the host system in diagnostic isolation and neutralization tests.

Major Findings: Previous reports have described a number of the general properties of the A-1 virus, an agent isolated from primary rabbit kidney cell cultures inoculated with an aliquot of the NIH icterogenic plasma pool. Of particular interest were the serological findings with specimens taken from volunteers who, a decade ago, developed serum hepatitis with jaundice following inoculation with several icterogenic materials, among which were aliquots from the NIH icterogenic plasma pool. Significant increases in antibody against the A-1 virus occurred in 93 percent of the thirty persons whose serial sera were tested.

When serial serum specimens were tested from volunteers who did not develop jaundice following inoculation with the same icterogenic materials, it was found that of the 17 persons from whom serum specimens were available before inoculation of infectious material, 14 possessed antibody against the A-1 virus in titers ranging from 1:10 to 1:40, with the majority at 1:20. These serologic studies suggest that these persons had had previous experience with A-1 virus and that this might account for the failure of clinical disease to appear.

Continuing attempts have been made to isolate transmissible agents from icterogenic materials, as well as specimens suspected of being icterogenic. Occasionally an agent has been isolated from such materials but subsequent studies have shown it to be a known microbiologic entity without a demonstrable serologic relation to human viral hepatitis infection.

A study has been initiated to determine the susceptibility of rhesus, vervet and cynomologous monkeys to infection with A-1 virus. Both inoculated and control monkeys are being followed using the following indices: observation for clinical disease, temperature, white blood counts, blood smears, rectal,pharyngeal and serum specimens and serial liver biopsies.

Many attempts have been made to obtain electron micrographs of A-1 virus both in infected cell cultures and in virus pellets prepared by ultracentrifugation. Results to date have been encouraging but not conclusive.

Paired and serial serum specimens from documented cases of viral hepatitis occurring in several geographic areas of the United States and abroad have been obtained and tested for A-1 virus antibody. Of the positive geographic areas, significant changes in A-1 virus antibody levels have been noted in specimens coming from Minneapolis, Minn. (1/2); Lewisburg, Kentucky (6/10); New Haven, Conn. (1/1; Somerville, N. J. (13/18); San Francisco, Calif. (1/1); Albany, N. Y. (1/4); Bethesda, Md. (2/20); Atlanta, Ga. (1/2); Cherokee, N. C. (2/3); Phildelphia, Pa. (2/3); Rio de Janeiro, Brazil (1/12); and Accra, Ghana (15/45). In particular, of 7 individuals in the Bridgewater, New Jersey area who developed viral hepatitis with jaundice, and from whom two or more specimens were available for testing, 6 showed fourfold or greater changes in A-1 virus antibody over a period of 3-6 months.

Significance to Bio-medical Research and the Program of the Division: The threat of epidemic hepatitis that constantly jeopardizes the health of both civilian and military populations coupled with the hazard of contamination of whole blood and blood derivatives with serum hepatitis virus makes the control of these diseases one of the major unresolved problems of contemporary virology.

Proposed Course of the Project: Serum specimens collected from hepatitis outbreaks will be used (1) in viral isolation procedures and (2) in neutralization tests to determine their content of A-1 virus antibody in order to serologically evaluate the relationship of A-1 virus to human hepatitis. Studies will be continued to further clarify the electronmicroscopic characteristics of this virus.

Part B included Yes/___/No/X /

Serial No. DBS 70
1. Virology & Rickettsiology
2. Virus Biology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Studies on antimicrobial agents in foodstuffs (Paolins)

Principal Investigator: Dr. C. P. Li

Other Investigators: Dr. Benjamin Prescott
Dr. Caspar W. Hiatt
Dr. J. B. Moloney
Dr. W. R. Green
Dr. R. H. Adamson
Elmer C. Martino

Cooperating Units: Laboratory of Bacterial Chemistry, NIAID
Laboratory of Biophysics & Biochemistry, DBS
Laboratory of Viral Oncology, Ophthalmology Branch, NCI
Laboratory of Chemical Pharmacology, NCI

Man Years (computed for the 18 month period)
Total: 7 1/2
Professional: 3
Other: 4 1/2

Project Description:

Objectives: (A) To attempt isolation of promising antiviral and/or antibacterial agents from foodstuffs, especially shellfish, which can be purified and concentrated for clinical trials; (B) To investigate (1) whether these substances are concerned in the defense mechanism of the host; (2) whether a balanced diet containing known quantities of such agents is useful in the treatment or prevention of bacterial and viral infections; (C) whether these agents have anti-cancer effects; (D) whether these antiviral agents can be used for further attenuation of live virus vaccines, such as Sabin type III live poliovaccine virus. The main project has been divided into the two subprojects.

Subproject I. Antimicrobial activity of shellfish fractions. The early studies of antibacterial paolin 1 and antiviral paolin 2 were published in the Transactions of New York Academy of Sciences (1962, v24, No. 5, p. 504).

To date five different antiviral or antibacterial paolins have been isolated from abalone, oyster and other shellfish (only the first two were previously reported).

Paolin 1. This is a glycoprotein, showing one peak on ultra-centrifugation with a sedimentation constant of 0.6S and a molecular weight around 5,000. It is isolated by chromatography (DEAE). Using the abalone material, it is usually found in the early eluates. When oyster material is used, it may occur in all the eluates. The yield is about 0.3%. It is antibacterial, 1 mg. containing about 25 units of antibacterial "paolin units."

Paolin 2. This is also a protein, but with a much larger molecule than paolin 1. When abalone or oyster material is passed through the DEAE cellulose column, this paolin is held back, but it can be washed down with molar NaCL. This paolin is antiviral.

Paolin 3. When the acetic acid extract of oysters is further purified by fractional precipitation with varying quantities of ethyl alcohol, a fraction is obtained which shows only one peak on ultra-centrifugation. It has a sedimentation constant of 1.6S and a molecular weight of about 10,000. The yield is about 0.5%. It is probably a mucoprotein. It is both antiviral and antibacterial, but it may be a mixture of several paolins. It inhibits herpes simplex virus in tissue culture.

Paolin 4. This is a histone or histone-like substance isolated from abalone and oysters by Dubos's method. The yield is about 0.8%. It has a sedimentation constant of 0.8S with a molecular weight of about 6,000. It is antibacterial.

Paolin 5. This is prepared by Szent-Gyorgyi's method for preparation of "retine." It is a small molecule, dialyzable but heat stable. It is most probably not a protein as it is soluble in chloroform. It is antibacterial, inhibiting the growth of S. aureus in vitro at a concentration of 1 PPM. It also showed marked therapeutic effect against S. aureus infection in mice after intra-peritoneal injection.

The acute and chronic toxicity of the acetic acid extract of oysters was studied in mice, cats, dogs and monkeys by oral and parenteral administration with doses varying from 20 mg/kg to 3 g/kg. No toxic signs were detected clinically or at necropsy, except that a transient leukopenia was observed in the large animals.

Subproject II, Isolation of antiviral and antibacterial substances from calf thymus. The results of this subproject were published (Proc. Soc. Exp. Biol. & Med. 1963, 114-504). Two kinds of extracts were made from calf thymus gland: in water, and in dilute acetic acid. The water extract inhibited Coxsackie A9 virus and type I poliovirus in tissue cultures and in mice. The acid extract showed in vitro anti-bacterial activity against S. aureus, S. pyogenes, organisms of the Pseudomonas group and certain other bacteria.

Significance of Bio-medical Research of the Program to the Division: Hopefully the paolins may offer an antimicrobial means of treatment and prevention of certain bacterial and viral infections.

Proposed Course of the Project: Various chemical methods will be used to concentrate and purify the antimicrobial substances under study. The final products will be assayed for in vitro and in vivo antibacterial activity and also in tissue culture, mice and rabbits for antiviral activity against influenza virus, poliovirus and herpes simplex virus. Mice will be fed crude and purified materials and then kept together with other mice infected with influenza virus to see whether contact infection can be prevented. Anti-cancer effect will be assayed in mice.

Arrangements have been made with Dr. J. A. Bell of NIAID to feed clam juice and/or oyster preparations to a number of children in Junior Village and observe them for the incidence of upper respiratory infections.

Attempt will be made to further attenuate type III poliovaccine virus by culturing it in presence of one of the antiviral agents.

Part B included Yes/X / No/ /

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Li, C. P., Prescott, B., Chi, L. L. and Martino, E. C.:
Antiviral and antibacterial activity of thymus extracts,
Proc. Soc. Exp. Biol. and Med.,1963, 114: 504-509.

Elected as Fellow of New York Academy of Sciences, Dec. 4, 1963.

Serial No. 71

1. Laboratory of Virology and Rickettsiology
2. Section on General Virology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Investigations Concerning Rubella Virus and Vaccine.

Principal Investigator: Dr. Paul D. Parkman

Other Investigators: Dr. Paul E. Phillips
Miss Nancy G. Rogers
Mrs. Barbara B. Jackson
Dr. Harry M. Meyer, Jr.

Cooperating Units: Walter Reed Army Institute of Research
Laboratory of Viral Immunology, DBS
Laboratory of Viral Oncology, NCI

Man Years:

Total:	4.5
Professional	2.25
Other:	2.25

Project Description:

A. Studies of the biological characteristics of rubella virus.

Studies of the characteristics of rubella in primary African green monkey kidney cell monolayers (GMK) begun at the Walter Reed Army Institute of Research, used its property of interfering with the cytopathic effect (CPE) of enteroviruses.

Utilizing this property for quantitation of virus, rubella virus infectivity was shown to be rapidly destroyed by ether, chloroform, formalin and heat. In filtration studies it appeared to be between 100 and 300μ in diameter. It differed from other human viruses with which it has these properties in common by failing to produce complement fixing of hemagglutinating antigens or CPE in other than primary human amnion or certain continuous rabbit kidney cultures (RK_{13}). These studies have been continued in attempts to 1) determine the nucleic acid composition of rubella virus and 2) evaluate culture techniques for detection of cytopathogenic effect.

Since virus titers were inadequate for direct chemical measurements of RNA or DNA, the effect of 5-iodo-2-deoxyuridine (IDU), an

inhibitor of DNA but not RNA-containing viruses was used. Rubella virus propagation rates and virus titers were unaffected by IDU-containing media; under these circumstances it behaved like RNA (poliovirus type 1, rubeola) and unlike DNA viruses (herpes simplex, vaccinia) tested simultaneously as controls. The failure of IDU to inhibit growth of rubella virus suggested that it was an RNA virus.

A number of cell culture systems have been evaluated for rubella virus cytopathic effect (CPE). While a number of cell cultures support growth, including BS-C-1, LLC-MK^2, Patas monkey kidney, human embryo kidney, rhesus monkey kidney, primary and continuous diploid rabbit kidney cells and WE-26, thus far only the RK_{13} line of continuous rabbit kidney cells described by McCarthy, et al (Lancet 2:593, 1963) has shown CPE. This technique has been found valuable principally for tests using virus adapted by 15 or more serial passages in the continuous rabbit kidney cell line. It was found that lowering incubation temperatures of infected cultures to 33°C and using medium without added serum, shortened the time required for appearance of rubella cytopathic effects in these cells by 3-5 days. Under these circumstances titration endpoints of adapted strains are stable by 10-12 days. Fluids harvested from RK_{13} cultures inoculated with high multiplicities of rubella virus show about 10-fold higher virus yields ($10^{5.5}$/0.1 ml) than similar harvests from GMK cultures.

With this system it has also been possible to recognize CPE in cultures inoculated with throat washings from rubella patients. The sensitivity of this cell line for primary isolation of rubella viruses appears to be comparable to that of the GMK-ECHO-11 virus interference system.

Using these cell cultures it has been possible to demonstrate rubella virus plaques in agar-overlaid cultures. Studies are currently in progress to determine the utility of this plaque assay system. Preliminary observations suggest that the efficiency of plaque formation is good and that it may be useful for studies requiring critical quantitation of virus.

B. Studies directed toward the standardization of serological tests for rubella.

To date the only tests for antibody to rubella virus are those employing rubella interference for enterovirus in grivet monkey kidney (GMK) cells or cytopathic effect (CPE) in human amnion or continuous rabbit kidney (RK_{13}) cells.

The results of these neutralization tests are influenced by a number of variables. Studies performed primarily in the GMK interference system indicate that factors important for reproducible antibody determinations include virus test dose, time of addition of the E-11 challenge virus and preincubation condition of serum virus mixtures. Results were also affected by addition of "accessory factors" contained in normal rabbit serum.

Rubella antibody titers are low in contrast with those of rubeola. With 2.0 log ID_{50} of rubeola virus, convalescent antibody titers are regularly 1:32 to 1:1024; against similar concentrations of rubella virus, antibody titers are seldom greater than 1:8 and biologically significant amounts of antibody can be missed. Lower concentrations of virus (1.3 to 1.7 log ID_{50}) allow detection of rubella antibody over a range of serum dilutions from 1:2 to 1:128. Neutralization tests performed with both animal and human sera indicated that a 10-fold increase in virus ordinarily produced a 4-fold decrease in antibody titer. The range of serum antibody titers against a similar test dose varied within 4-fold, from one test to another. This was similar to the variation observed in rubeola virus neutralization tests. Addition of E-11 challenge virus at 10 days, when rubella virus titration endpoints were stable, resulted in lower antibody levels than in tests challenged earlier.

Studies comparing the effects of preincubation on serum virus mixtures showed that at 37°C essentially all neutralization occurs during the first hour. Neither 4°C or 25°C for one hour, nor prolonged pre-incubation at 4°C with or without a prior 37°C period, enhanced antibody titers. The addition of unheated antibody-free rabbit serum in final volume concentration of 5% to serum-virus mixtures potentiated antibody titers by from 2 to 8-fold; the effect was evident in tests in which E-11 challenge was delayed until 10 days, but showed less enhancing effect in tests challenged earlier. In preliminary studies these factors appear also to be true for the RK_{13} cytopathic system.

From these experiments, current methods for measuring neutralizing antibody in the GMK-E-11 virus interference system employ a 37°C, one-hour incubation period, titration of serial 2-fold serum dilutions against an estimated 1.5 log InD_{50} dose of rubella virus, and addition of E-11 challenge virus after cultures have been incubated five days.

Experiments are in progress to determine the relationship of results of these tests with those derived from the RK_{13} cytopathic system. Preliminary observations show that in the latter system, rubella virus doses from 1.5 to 2.5 ID_{50} can be used without sacrificing test sensitivity or reliability. These results also suggest that the RK_{13} cell line may be of considerable value for rubella neutralization test.

C. Studies of natural rubella infections of man.

The reliability of the rubella virus neutralization test for detection of human serum antibody was examined by repeated testing of human sera obtained before infection and at varying times after convalescence from the disease. In neutralization tests with carefully controlled virus doses (optimally 1.0 to 1.7 log InD_{50})sera obtained in convalescence uniformly contained antibody. In contrast, antibody was not demonstrable in sera obtained prior to either overt or clinically inapparent infection. It was possible to test the accuracy of screening tests for rubella antibody in sera collected from a military recruit training company in which frequent collection of specimens made it possible to identify all rubella infections by recovery of virus from throat washings or by serologic evidence of infection. In screening tests a 1:2 dilution of serum was tested against virus doses calculated to be 10 and 100 InD_{50}. Those without antibody at a 1:2 dilution were predicted as susceptible, those with antibody as immune. These predictions were then compared with observed natural infections. The errors in prediction of susceptibility or immunity were increased in the dosage range less than 1.0 or greater than 2.0 log InD_{50}. Within this range, error in detecting immune status was approximately 10%. Continued experience showed that screening test accuracy was improved by the inclusion of low and high titered antisera as well as antibody free samples as controls on the test dose of virus itself. In tests interpreted on this basis, accuracy of identification of immunologic status approached 100%.

Rubella antibody appeared promptly after infection in seven of fifteen sera collected from patients on the first or second days of rash. Low antibody levels of 1:2 to 1:4 were present. Antibody titers in these, and in patients with inapparent natural infections increased thereafter, and at 20 to 30 days ranged from 1:8 to 1:64. Persistence of antibody was suggested by findings that 1) levels in sera obtained six months after infection showed titers similar to those in immediate convalescence; 2) antibody levels in immune adults remained unchanged in sera drawn from three to eight years apart; 3) antibodies were present in the sera of elderly veterans.

These data suggest that detectable circulating antibody to rubella are associated with immunity and that immunity resulting from infection may be lifelong.

D. Studies of rubella virus antigenicity.

It was possible to produce rubella virus antibody by repeatedly inoculating rabbits or guinea pigs with infectious rubella virus. In these experiments three or more 1 ml inoculations of clarified tissue culture fluids containing 3.0 to 4.0 log InD_{50}/0.1 ml virus induced low levels of neutralizing antibody in all animals tested. Attempts were made to assess the antigenicity of similar preparations rendered noninfectious by treatment with formalin. In these experiments, formalin was added in 1:4000 final concentration to virus preparations; these were then filtered through Millipore membranes (300μ apd) and allowed to react at 4°C or 37°C. Inactivation rates at 37°C (normally approximately 0.3 log units/hour) were markedly increased by formalin, so that residual infectivity could not be detected after two hours in any of three different inactivation experiments. At 4°C formalin inactivation was much slower and incomplete even after 10 days.

Guinea pigs and rhesus monkeys, immunized with one to two ml doses of virus inactivated by treatment with 1:4000 formalin at 37°C for 24 hours failed to show antibody response. This was in contrast to the prompt antibody response of other guinea pigs immunized at the same time with un-inactivated virus or with preparations treated with formalin at 4°C, containing small amounts of infectious virus. Formalinized virus concentrated 10-fold or incorporated with Freund's adjuvant did not produce detectable circulating antibody in rhesus monkeys similarly immunized. Immunized monkeys were not resistant to rubella infection upon subsequent challenge with live virus.

The failure to induce antibody is probably related to lack of sufficient antigenic mass; perhaps excessive denaturation of virus protein by formaldehyde also played a role. Studies directed toward testing more concentrated virus preparations, inactivated by a number of different methods, are currently in progress.

E. Studies of possible rubella virus oncogenic effects.

The suggestion that the morphology of rubella virus resembled that of rodent leukemia viruses by Norrby, et al (Archiv. Gesamte Virusforschung 13: 421, 1963) stimulated interest in the possible production of leukemia or other tumors in experimental animals. In conjunction with Dr. John B. Moloney of the Laboratory of Viral Oncology, National Cancer Institute, a leukemia-sensitive strain of mice was inoculated with rubella virus.

Randomized litters of newborn BALB/c mice were inoculated by the intracerebral, intraperitoneal or subcutaneous routes with either rubella virus, concentrated and partially purified by ultracentrifugation, or control GMK tissue culture fluids prepared similarly. At one month of age, mice were weaned and redistributed in cages by sex and route of inoculation. In addition, litters of suckling hamsters have been inoculated intraperitoneally with the same material. Animals are being examined once weekly for evidence of apparent illness or appearance of tumors. At the present time, four months after inoculation, all animals which survived the newborn period appear healthy; no tumors have appeared. Observation of these animals is planned for one year from time of inoculation.

F. Study of rubella in monkeys.

Since monkeys had been shown to be suitable host for a number of human viruses, including rubeola, the ability of rubella virus to produce infections in these animals was tested. Preliminary screening of sera suggested that unlike rubeola, rubella antibody occurred infrequently under usual transportation and housing conditions, since only 1 of 15 rhesus monkey sera tested contained antibody. Subsequent studies of sera from rhesus monkeys subjected to special handling procedures designed to prevent acquisition of rubeola antibody have shown a similar low incidence.

In attempts to induce experimental infections, animals have been inoculated by intravenous or intramuscular routes. No rash, lymphadenopathy, respiratory symptoms or elevations in temperature attributable to rubella virus infection have been observed in any of nine rhesus or two cercopithecus monkeys inoculated with tissue culture rubella virus at the third or fourth passage level. All inoculated animals, however, shed virus and subsequently developed neutralizing antibody, indicating that subclinical infections had occurred.

Virus was recovered from swabs taken from the nose, conjunctivae, pharynx and rectum and from whole blood or serum. Virus recovery from these specimens resemble in general, that observed with natural human infections; virus was most frequently recovered from blood or serum from the 4th to the 9th day after inoculation, but never after detectable neutralizing antibody appeared. Virus was recoverable from throat washings as early as four days after inoculation. Virus was recovered from swabs of all animals' respiratory secretions. The throat yielded virus occasionally even within a day or two after antibody appeared. Isolates from other sources were less frequent; viremia was demonstrated in one or more specimens from six of nine rhesus monkeys. Virus was irregularly present in rectal swabs. Recovery from this source was made as long as 16 days after inoculation and thus did not appear to be related to presence of antibody as was virus in serum and throat washing.

Presence of neutralizing antibody at the time of inoculation in animals infected three months previously prevented subsequent recovery of virus from any source, even when large (4.4 log InD_{50}) inocula were employed.

Significance to biomedical research and the program of this Division: All work of this Section pertaining to rubella is potentially useful in resolving problems which may occur in the development and testing of rubella vaccines.

Proposed Course: A major effort along these lines will be continued.

Part B included yes /X/ no /___/

Part B. Honors, Awards and Publications.

Parkman, P.D., Buescher, E. L., Artenstein, M. S., McCown, J. M., Mundon, F. K,, Druzd, A. D.: Studies of Rubella I. Properties of the Virus. J. Immunology, in press.

Parkman, P. D., Mundon, F. K., McCown, J. M., Buescher, E. L.: Studies of Rubella II. Neutralization of the Virus. J. Immunology, in press.

Serial No. 72

1. Laboratory of Virology and Rickettsiology
2. Section on General Virology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Investigations Concerning the Smallpox Group of Viruses and Smallpox Vaccine.

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators : Miss Nancy G. Rogers
Mrs. Barbara C. Bernheim

Cooperating Units : Ministry of Health, Republic of Upper Volta

Man Years:

Total:	1.5
Professional:	0.75
Other:	0.75

Project Description: A. Clinical studies with smallpox vaccine.

(1) Titration of smallpox vaccine in man. During the fall of 1963 our group conducted a smallpox vaccine study in Bobo-Dioulasso, Upper Volta. Our objectives were to determine: (a) the infectious $dose_{50}$ (ID_{50}) of the DBS Reference Smallpox Vaccine Lot 2 when percutaneously administered to susceptible children and (b) the ID_{50} of the vaccine when jet inoculated. We were assisted in this study by Upper Volta Health Ministry personnel.

One hundred children with no previous history of smallpox vaccination were divided into two groups. Members of the first group were inoculated with various dilutions of vaccine by the conventional multiple pressure technique. Children in the other group were jet inoculated with similar dilutions of the same vaccine. Serum specimens collected from participants before and four weeks after vaccination were tested for smallpox antibodies. Children were asked to return at periodic intervals so that skin reactions could be observed.

The ID_{50} of the vaccine was calculated in two ways. The first method involved a titrational estimation based on the cutaneous response to vaccination. This will be referred to as skin reactive $dose_{50}$ (SRD_{50}). The other method of calculation was based on seroconversion of susceptible children. This will be referred to as the immunological infectious $dose_{50}$ (IID_{50}).

The results obtained in children vaccinated by scarification indicated that with percutaneous inoculation the SRD_{50} and IID_{50} were essentially the same, i.e., $10^{-2.6}$ and $10^{-2.4}$ respectively. On the other hand, jet inoculation gave quite a different picture. Here the SRD_{50} was $10^{-3.6}$ while the IID_{50} was greater than $10^{-6.4}$. It may be noted that the titer of this vaccine for cell cultures is $10^{-7.7}$/0.1 ml and for eggs (CAM) is $10^{-8.2}$/0.2 ml. Thus, while by scarification it requires on the order of 100,000 CAM ID_{50} of vaccinia virus to infect 50% of susceptible children, it requires less than 100 CAM ID_{50} to effect seroconversion with jet inoculation.

Significance to bio-medical research and the Program of the Division:

All of this work directly pertains to research problems in the control of smallpox vaccine.

Proposed Course: These data open several new avenues of investigation concerning immunity to smallpox which we plan to explore.

Part B included yes /__/ no /X/

Serial No. 73

1. Laboratory of Virology and Rickettsiology
2. Section on General Virology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title : Investigations Concerning Measles Virus and Vaccine.

Principal Investigator: Dr. Harry M. Meyer, Jr.

Other Investigators : Miss Nancy G. Rogers
Mrs. Barbara C. Bernheim
Mrs. Barbara B. Jackson
Dr. Daniel D. Hostetler, Jr.
Dr. Paul E. Phillips

Cooperating Units : Laboratory of Viral Immunology, DBS
Agency for International Development
Ministry of Health, Republic of Upper Volta
L'Organization de Coordination et de Coopération pour la Lutte Contre les Grandes Endémies.

Man Years:

Total:	10.0
Professional:	4.0
Other:	6.0

Project Description:

A. Clinical studies with live measles vaccine. In November, 1961 our group began a series of clinical studies in West Africa using the Enders "B" level live, attenuated measles vaccine. The initial pilot study (November, 1961--January, 1962) established that the African child, although beset by many health problems, responded to inoculation of the live vaccine with or without gamma globulin in the same manner as his American counterpart. These observations were of keen interest to indigenous health officials since natural measles may be associated with a 25 to 50% mortality during West African epidemics.

During the period covered by this annual report four additional field studies have been completed and will be described in the following paragraphs.

(1) Immunization with combined live measles, smallpox and yellow fever vaccines. In West Africa smallpox and yellow fever are

controlled by mass vaccination, yet even these relatively simple preventive medicine programs are frequently compromised by budgetary considerations and a shortage of trained personnel. To offset certain of these problems combinations of smallpox and yellow fever vaccine have seen extensive field use in French-speaking West Africa for over a decade.

It was felt that jet inoculation of a combination of these two vaccines with live measles vaccine, if proved safe and efficacious, might provide a still more attractive solution. At the request of the Minister of Health, Republic of Upper Volta, a pilot study was designed to investigate the feasibility of triple vaccination.

Children participating in the study were selected on the basis of having no history of experience with any of the three viruses. These children were divided into five groups of approximately 100 each. The first three groups were jet-inoculated with one or another of the monovalent vaccines (measles, smallpox or 17-D yellow fever) while the fourth group received a measles-smallpox mixture and the final group was inoculated with the trivalent combination.

Surveillance carried out over a three week period indicated that combining the vaccines did not potentiate or otherwise alter the characteristic clinical response elicited by each component virus. Individuals receiving vaccinia virus alone or in combination exhibited the typical cutaneous reaction associated with primary smallpox vaccination.

Serologic tests were performed on specimens collected from children before and four weeks after vaccination. As was anticipated from their history, most vaccinees possessed no antibodies for any of the three viruses before vaccination. Seroconversion rates were uniformly good and unaffected by combining the vaccines.

It was concluded that combined live measles, smallpox and 17-D yellow fever vaccines could be safely and effectively administered to triple-negative children by jet inoculation.

(2) Mass vaccination against measles in Upper Volta. After evaluation of the results of the original Volta pilot study, the Minister of Health urged us to consider expanding the experimental program. Specifically he proposed that we undertake a country-wide mass vaccination study using the Enders live measles vaccine without gamma globulin. At that time the total clinical experience with the Edmonston attenuated strain of measles virus was limited to observation of about 20,000 recipients (most of these were healthy American school-age children) and it was felt that a mass campaign

in a developing country would provide needed scientific information as well as being of broad public health interest.

The study was designed as a collaborative venture of NIH, AID and the Health Ministry of Upper Volta. During the course of the combined vaccines pilot study (described in the preceding section) African male nurses were trained to operate jet guns, generators and other special equipment to be used in the mass campaign. Between November 5, 1962 and March 5, 1963 eight African teams supported by an NIH team covered the nine medical sectors of Upper Volta, jet inoculating 731,000 with live measles vaccine. It was estimated that the program reached about 90% of all children six months to five years of age, i.e., the age group comprising most of the population at risk.

As these figures indicate, the vaccine was eagerly sought by the population and the mobile teams were able to penetrate and operate effectively in even the most remote sections of the country. The expected febrile reaction to the vaccine was well accepted by parents. No unusual reactions, such as encephalitis, were observed. Clinical surveillance was for the most part crude, since 95% of the population is rural. Modern hospitals in Ouagadougou and Bobo-Dioulasso serve areas encompassing about 25,000 vaccinees, thus it is worth noting that these hospitals did not experience any increase in pediatric mortality due to infectious diseases during the period of vaccine reactions.

Measles is a reportable disease in Upper Volta. Analysis of the statistical data which have accumulated since March, 1963 indicates that there has been a pronounced overall reduction in the incidence of measles. This has been especially prominent in vaccinated children, i.e., of 4,396 cases of measles reported in the months April, 1963--February, 1964 inclusively, only 129 cases occurred in vaccinated children.

These results have furnished valuable information on both the safety and the efficacy of live measles vaccine under conditions of mass immunization in an area where natural measles is characterized by extremely high mortality.

(3) Titration of live measles vaccine in man. During the fall of 1963 our group participated in a fourth Upper Volta clinical study. This project was designed to gather several bits of practical information.

It is a responsibility of the Division to assay the potency of commercial live measles vaccine. These tests, performed in BS-C-1 cell cultures, are the basis for releasing or rejecting individual lots of vaccine. Consequently, we were interested in comparing the

titer of the live vaccine in susceptible children with that obtained in the BS-C-1 cell culture system. In addition, since it seemed likely that several developing countries would administer the vaccine by jet inoculation, we felt that the titration of the attenuated measles virus in man by jet gun, as compared to needle and syringe was in order.

The study was conducted in the Bobo-Dioulasso area with the cooperation and assistance of Volta Health Ministry personnel. A total of 117 children were inoculated with various dilutions of vaccine with either syringe or jet gun. Tests on paired pre- and post-vaccination sera formed the basis for determining the vaccine titer in the human host.

The results indicated that the infectious $dose_{50}$ (ID_{50}) of the vaccine for man and for BS-C-1 cell cultures was virtually identical. Also, no significant differences in ID_{50} were obtained when the vaccine was administered by jet gun as compared to syringe. Specifically with the lot of commercial vaccine used, the ID_{50}/0.5 ml were as follows: BS-C-1 cells, $10^{-3.8}$; children by syringe and needle, $10^{-3.6}$; and children by jet gun, $10^{-3.9}$.

(4) O.C.C.G.E. measles vaccination project. Between September, 1963 and January, 1964 our group directed a West African regional measles control program which was jointly sponsored by AID and L'Organization de Coordination et de Coopération pour la Lutte contre les Grandes Endémies. The program was designed to provide a backlog of experience that would aid in the formulation of long term regional plans for measles control.

This was a two-step program. Initially, male nurses from seven OCCGE-member West African nations were trained in methods of jet inoculation and other technology used in measles field studies. The training program was conducted at the Centre Muraz, a research and teaching center of the OCCGE, located in Bobo-Dioulasso. In the second step each country was visited in turn in a vaccine demonstration program. About 15,000 doses of measles vaccine were administered in a previously selected area of each country, using mass inoculation techniques and employing the nurse-trainees to deliver the vaccine.

The program was considered highly successful. As a product of the training program, the nurse-trainees performed very well in the field with a minimum of direct supervision. Although the vaccinated populations comprised several distinct ethnic groups, all were receptive to the program and accepted the clinical reaction elicited by the Enders vaccine without incident. Post-vaccination serum samples were collected in Mali, Guinea, Mauritania, Niger and Senegal. Serologic tests completed to date indicate that 96 to 100% of the vaccinated populations are now immune. Preliminary

epidemiologic reports support these findings in that measles has apparently been well controlled in the vaccinated areas.

B. Studies directed toward standardization of serologic tests for measles. The comparison of serologic data obtained by neutralization and hemagglutination inhibition (HAI) tests is continuing. These results will be subjected to a detailed analysis during the coming year. In general, the HAI antibody titer of a given serum or gamma globulin specimen tends to be 2 to 4-fold higher than the corresponding neutralizing antibody titer. The lowest dilution of serum that can be assayed by the HAI procedure is 1:2 while undiluted serum can be tested for neutralizing antibody. As a result the two tests in routine practice are of comparable sensitivity in detection of minimal amounts of measles antibody.

Because of the economy and simplicity of the measles HAI test (as compared to virus neutralization) it offers considerable promise in the field of biologics control.

C. Markers of virulent and attenuated measles virus in rhesus monkeys. This work has been continued both to satisfy control obligations for monkey neurovirulence testing of candidate virus strains for new live measles vaccines and to obtain additional information relating to the biological characteristics of simian infection with attenuated measles viruses.

Five experimental live, attenuated measles virus strains have been tested to date by intracisternal and intrathalamic inoculation of measles-susceptible rhesus monkeys. This work is still in progress but thus far all the live measles vaccines tested share the following properties in monkeys: (a) no communicability even to cage contacts, (b) no detectable viremia or respiratory excretion of virus, (c) no gross or microscopic evidence of CNS pathology (these determinations were made by Dr. R. Kirschstein of LVI, (d) good immunogenicity as indicated by seroconversion of 100% of inoculated monkeys and (e) no overt disease in infected animals.

Significance to biomedical research and the program of this Division. All work of this Section pertaining to measles is directly concerned with problems of control of measles vaccine as well as evaluation of its safety and efficacy among children in developing nations.

Proposed Course of project. Work will be continued along the lines described.

Part B included yes /X/ no / /

Part B Honors, Awards, and Publications

Meyer, Harry M., Jr., Hostetler, Daniel D., Jr., Bernheim, Barbara C., Rogers, Nancy G., Lambin, Paul, Chassary, Albert, Smadel, Joseph E.: Response of Volta Children to Live Attenuated Measles Virus Vaccine. Bul. WHO in press.

Meyer, Harry M., Jr., Hostetler, Daniel D., Jr., Bernheim, Barbara C., Rogers, Nancy G., Lambin, Paul, Chassary, Albert, Labusquière, René, Smadel, Joseph E.: Responses of Volta Children to Jet Inoculation of Combined Live Measles, Smallpox and Yellow Fever Vaccines. Bul. WHO in press.

ANNUAL REPORT
(January 1, 1963 - June 30, 1964)

DIVISION OF RESEARCH FACILITIES AND RESOURCES

NATIONAL INSTITUTES OF HEALTH

INTRODUCTION

In the 18 months covered by this report, the Division of Research Facilities and Resources welded into a functioning unit five programs that had been dispersed throughout NIH. These programs, with a total budget of $133,306,000, have a common purpose of supporting large-scale facilities that contribute to the excellence of research in one institution, or several institutions within a region, or to segments of the scientific community through a national resource such as the National Conditioning Primate Research Center and the Medical Data Processing Research Center.

The five DRFR programs are: health research facilities, general clinical research centers, general research support, special research resources, and animal resources. In 1964, a sixth program, scientific and technical research resources was authorized, but implementation has been delayed by executive decision.

Administering these programs under the rules applied to project grants aggravates problems that are inherent in the administration of center grant operations. Unlike project grants, those administered by the Division require extensive negotiation because of their complexity, scope, and the large sums of money involved. Not only must the scientific merit of multidisciplinary research projects be evaluated, but, as in the case of a research building, the exact amount of square feet for which HRF funds may be granted, in line with requirements in the law. In some instances, a total biomedical program, including its future potential, must be reviewed and evaluated. The multidisciplinary, multicategorical aspects of research facility and resources grants require administrative staff competence of exceptionally high order. Recruiting such staff has been a problem of the first magnitude.

The Division, while furthering its own program aims, is responsible for furthering those of the National Institutes of Health and, upon occasion, those of other components of the Public Health Service, such as the Division of Environmental Health. Close coordination and collaboration has been maintained with these components, especially with NICHHD, NIMH, NIDR, NCI, and NIGMS. The dual responsibility of DRFR and NICHHD for the mental retardation research center program requires continuing liaison on many levels, including the dual grant application review by two Councils, site visits, and staff consultation on negotiations of applications.

With the enactment of the Health Professional Schools legislation, DRFR has worked closely with the Bureau of State Services in planning an orderly implementation of the program as it involves health research facility

construction with multiple program responsibility over 10 or more years.

Indicative of the complexity of the Division's operations is the fact that review of grant applications, program policy review, and recommendation is divided among three national advisory groups: National Advisory Council on Health Research Facilities (health research facilities), National Advisory Health Council (general research support), and the National Advisory Research Resources Committee (general clinical research centers, special research resources, and animal resources). Aside from the normal preparations necessary for all Council meetings, DRFR administrative staff has had to triple its time and effort in keeping the three groups mutually informed of program activities, in presiding at meetings and making presentations, and in continuing liaison.

The size and complexity of applications for health research facilities grants are now such that several changes have had to be made in the functions of the Branch to streamline operations and to ensure greater program and fiscal control. When the program began in 1956, grants were relatively small and frequently provided improved laboratories for only a small group of scientists. Council review of these applications was rather uncomplicated; most Council members knew personally, or by reputation, the scientists who would be conducting research in the proposed facilities. The situation has changed markedly in the past 18 months. The trend is toward large-scale construction, often designed to house hundreds of scientists. Another development is requests for specialized research facilities such as radiation centers, biotrons, and high altitude chambers. Modern research equipment often requires special construction. These factors have vastly complicated the review of health research facility applications and have limited the ability of the Council to devote more time to pressing policy matters of national consequence in the health research construction program. Thus, a remedy was clearly necessary.

To assist the Council in coping with the formidable workload of reviewing scores of applications and making site visits that frequently take two days at one institution, DRFR in April 1964, established a Scientific Review Committee for Health Research Facilities. Comprised of some of the Nation's top scientists, the Committee will concentrate on the evaluation of proposed research programs for which facilities are requested and upon the suitability of the facilities for those programs. The Committee will make recommendations to the Council and to the Surgeon General.

A further measure to strengthen the health research facilities program, as well as other Division programs, is the development of the Office of Architecture and Engineering to provide professional review and appraisal of research facility design and costs. To assist grant applications and ensure conformance to government regulations, the Office of Architecture and Engineering (A & E) developed the following guidelines and procedures:

1. A Program of Requirements document which must accompany each research facility construction grant application which describes functional needs of the proposed facility, space allocation for specific research programs, design criteria for each program area, and an explanation of the architectural-engineering concept

of the structure. A cost breakdown is included.

2. A preliminary guide for applications in preparing architectural engineering documents to be submitted with the application.

3. A systematic review of the schematic, preliminary, and final working drawings.

4. A summary table for applicants to list their allocation of space, fixed and movable equipment and personnel for the various scientific disciplines.

5. A determination of estimated construction costs prior to the final award of grant funds. (This has resulted in a significant number of cost redeterminations. See Tables II and III.)

6. A certification of completion of construction is now required signed by the responsible architect in a standard report which attests that the structure has been completed in accordance with the approved plans and specifications. Alternate methods of final inspection by contract or by the engineering staff are available for projects where problems have developed during the process of construction.

Table I

Summary of Architectural and Engineering Plan Reviews for Branches of the Division

	HRFB	GCRCB	SRRB
Application A & E Documents Reviewed	156	8	4
Intermediate Design Reviews	40	-	-
Final Working Drawings Reviews	50	4	1
Totals	246	12	5

Summary of Final Estimated Total Construction Costs

	HRFB	GCRCB	SRRB
Final Necessary Construction Costs	41	6	1

When adjustments or corrections in design are involved, application drawings require from two to three reviews--a preliminary review, a request for more information or adjustments in the design, and a final review to correlate the corrective information with the original application drawings. The 246 application drawings reviewed, therefore, involved approximately 350 individual actions by the architectural-engineering staff.

The technical design and construction reviews by the architectural-engineering staff has resulted in significant financial changes in the construction budgets. In some instances, institutions have been advised that their cost estimates appeared low and have been requested to recheck their estimates to insure that some critical items of the design had not been overlooked. On the other hand, after A & E review, some cost estimates have been reduced without impairment of the approved research functions. Savings have been achieved through the following types of actions by the architectural-engineering staff:

1. Technical assistance
2. Review of application drawings and associated documents
3. Review of bidding documents (final working drawings)

The following criteria are used to judge when savings are effected:

1. When an institution has obtained the full functional requirements of their facility, including the research program, at a cost less than estimated prior to the technical advice from this office.

2. When the architectural-engineering staff recommended a lower construction cost estimate after review of application drawings and the recommendation was sustained by the National Advisory Council on Health Research Facilities.

3. When PHS participation in construction costs has been reduced as a result of architectural-engineering staff review of the bidding documents and subsequent recommendation.

The following tables summarize the cost reductions achieved without impairment of design since approximately December 1963 when this type of review became active. Cost reductions that would have occurred under the program policies existing before this Office of Architecture and Engineering was established could not accurately be determined and, therefore, have not been included.

Table II

Cost Reductions from Review of Application Drawings

Project	Institution	Amount requested by applicant	Amount recommended by A/E Office	Amount recommended by Council	Saving
FR-03133	Univ. of Pa.	$302,224	$194,225	$194,225	$107,999
FR-03087	St. Louis State Hosp.	$116,918	$ 67,420	$ 67,420	$ 49,498
FR-03070	Mt. Sinai Hosp. New York	$159,100	$ 92,761	$ 92,761	$ 66,339
FR-03007	U. of Missouri	$350,730	$316,037	$229,324	$ 34,693
FR-03103	Harvard Univ.	$232,500	$151,000	$151,000	$ 81,500
			Subtotal		$340,029

Table III

Cost Reductions Resulting from the A/E Review of Bids Received

Project	Institution	Award by Council	Recommended by A/E Office	Saving
FR-03063	U.Y. Univ.	$157,545	$145,855	$ 11,690
FR-03048	Yale Univ.	$ 50,333	$ 38,007	$ 12,326
FR-03080	Harvard Univ.	$ 93,938	$ 87,989	$ 5,949
RC-955	Albert Einstein University	$636,000	$507,638	$128,362
RC1171	Washington State University	$106,400	$102,914	$ 3,486
FR-03020	Harvard Univ.	$197,000	$138,000	$ 59,000
FR-03017	Illinois Univ.	$750,000	$734,987	$ 15,013
RC-1188	Childrens Hosp. Chicago	$900,000	$867,346	$ 32,654
			Subtotal	$268,480
			Total for all reductions	$608,509

Future plans include the development and issuance of design criteria and standards, including unit costs for different types of research facilities and equipment. Work on this project has begun, but it will probably be early in 1965 before adequate information can be produced with the available staff.

A new revised version of the A&E Guide for preparing the architectural documents for research facility construction grants applications is being prepared and should be completed by mid 1964.

If additional positions are available in FY '65, it is planned to make final inspections on the completed construction of all large projects where there have been questions during the design and construction phases.

The long range objective of the A&E Office is the development of excellence in the design of research facilities among the architectural-engineering professions. The Office should provide leadership in stimulating interest and research activity in the design of these specialized facilities without placing responsibility for the design competence in the PHS. A major effort of the A&E Office has been to increase the effective participation of the architect and engineer during the early planning phases of the project when many basic decisions are made about cost, size and nature of the facility. This participation is intended to assure everyday plan reviews and cost evaluations which are the requirements of responsible administration of public funds as well as an effective, attractively designed facility which efficiently serves the needs for which it was designed.

To improve methods of accountability for funds and provide better control of program data, DRFR established a Program Analysis Office in September 1963. During the ensuing nine months, the Program Analysis Office developed program reports for the General Research Support Branch and assessed the availability, reliability, and significance of program information received by the five Branches of DRFR.

A complete set of codes and procedures has been developed for the General Research Support program and a reasonably elaborate retrieval for the first GRS program year (1962) has been incorporated into decks of punched cards. Coding for GRS is now in progress for 1963. By October of this year comprehensive program analysis in considerable detail will become a reality for GRS.

Concurrently, plans are being developed for bringing the other Branch programs into the Division's over-all statistical system. The General Clinical Research Centers analysis is scheduled to begin in August, and that for Health Research Facilities late in 1964. Since some of the programs have an eight years' backlog of grant files, the initial data capture operation is a major undertaking. Coding should be completed for all Division programs by mid-1965, unless a major push is decided upon involving serious scientific program operation complications and/or personnel recruitment.

Future plans are to maintain an integrated data retrieval and program analysis activity for the entire Division. The Program Analysis office will also take part in program planning and evaluation, and has a major responsibility in the implementation of special studies and surveys, preparation of special reports, and analysis of program trends.

Individual reports on each of the Division's Branches follow:

ANIMAL RESOURCES BRANCH

Program Goals

The Animal Resources Branch supports animal resources, regional primate research centers and encourages research in the basic problems of diseases of research animals.

The major program activity of the Branch is the administration of grants for the construction and operation of seven regional primate research centers.

Accomplishments

In the past 18 months, in addition to administering the primate center program, the Branch:

1. Developed a comprehensive program proposal to help meet the national needs for laboratory animal resources

2. Assisted the Division's Health Research Facilities program evaluate applications for construction funds for animal facilities

3. Programmed and awarded within the limits of Division funds a modest number of carefully selected animal resource grants

4. By special arrangement, administered several animal resource grants funded by other NIH Institutes

5. Established an Advisory Committee on Animal Resources

6. Was designated as the official focal point for answering inquiries on laboratory animals for the PHS

7. Furnished consultation to institutions on laboratory animal care problems

8. Reviewed for the PHS and NIH the "Guide for Laboratory Animal Facilities and Care"

9. Participated with the National Science Foundation in development of collaborative primate programs with the Japanese.

On October 10 and 11, 1963, the first meeting of the Regional Primate Research Center Directors was held at NIH with all center directors and key university officials. A second meeting of the center directors was held on April 27 and 28, 1964 at Madison, Wis., at the official dedication of the Wisconsin Regional Primate Research Center. At the suggestion of a center director, a committee was appointed to study the practicability of an integrated computer system into which data from all seven centers could be fed. These data could be used for individual requests and for comprehensive analyses of research findings and demographic information on the primates.

Staff members of the Branch made 13 site visits for the Division's Health Research Facilities Branch to institutions planning to build new animal quarters.

The Branch has assisted various institutions in developing applications for animal resources. Twenty-seven applications assigned to the Branch, 14 of which were recommended for approval, cover subjects such as the support and improvement of animal facilities in medical schools; study of the development and breeding of species or strains of animals that show promise of being valuable research tools; support for the maintenance of strains of animals uniquely suited to certain kinds of research, such as tissue transplantation; and research on some major diseases of laboratory animals.

Before the establishment of this Branch, several NIH Institutes supported research animal programs which cut across disciplinary lines. By mutual agreement, the Animal Resources Branch now administers such grants and will fund them when money becomes available.

At the first meeting of the Advisory Committee on Animal Resources on October 29, 1964 at the NIH, members were asked to evaluate the Branch's proposed program and to make suggestions. In the future, this committee will review specific projects, and make recommendations concerning program policies and direction.

In April 1964, the Branch was assigned the responsibility for answering all correspondence on animal care, especially laboratory animals, referred to the DHEW by Congress, the White House and others. The number of letters, many of which are caustically critical of NIH, runs as high as 85 a week.

Replies require great tact in most instances and, in some, professional and technical background.

The Branch receives requests for information from institutions throughout the country on research animal facilities, on problems of animal care, and on suitable personnel to fill positions in biomedical research institutions.

The Branch Chief has been appointed chairman of NIH Committee to review the booklet "Guide for Laboratory Animal Facilities and Care" distributed to all NIH grantees.

The Branch Chief was a participant at the Planning Meeting on Primate Biology of the U.S.-Japan Cooperative Program in Science which met in Japan in February 1964. Sponsored by the National Science Foundation, this meeting was a most successful first step in collaboration between these two countries in the study of primates.

Following are summaries of accomplishments in the primate research center program:

Oregon Regional Primate Research Center - University of Oregon

The Oregon Center, completed in December 1962, is in full operation. Because of a change in Directors early in 1963, programs came to a halt in some areas and changed in others. The present Director, in the early part of 1963, devoted much of his effort to building a research staff and in replenishing the depleted primate colony with a very productive breeding program. The Center is now functioning at almost peak activity. The primate colony, reinforced by many new animals, is in excellent condition, and the breeding program underway.

In process are computer experimentations in biomathematics, data analysis and animal records. Visiting scientists from this country and abroad are conducting many projects at the Center and assistance in several problems has been given to scientists in other institutions in the region. Some areas of research are embryology and developmental biology, cardiovascular diseases, cutaneous biology, physical anthropology, oncogenic viruses and immunochemistry. Two electronic technicians serve the Center in developing electronic instrumentation. Future plans include a modest program in bioengineering within the Center.

From March 4, 1963 to February 29, 1964, 238 experimental procedures were performed on 189 animals. All surgery was performed by or under the direction of staff surgeons or veterinarians.

Sixty-three scientific papers were published during the past year by members of the Center staff.

Yerkes Regional Primate Research Center - Emory University

Ground breaking ceremonies for construction of the new Center took place December 30, 1963, and construction has begun. The Center's field

station is expected to be completed by September 1964, and the main Center by January 1965.

Meanwhile, research has proceeded at the Yerkes Primate Research Laboratory, Orange Park, Florida, and in temporary quarters at Emory. At Orange Park, the primate colony numbers 160, including simians, orangutans, chimpanzees and lowland gorillas. Six pyschologists on the staff are working on behavioral studies of primates. Several staff members have visited Borneo, Japan, and Puerto Rico to study primates in their native habitats. On the Emory campus, anatomical studies are being carried out. A collaborative study is being conducted with Harvard School of Public Health on the induction and prevention of atherosclerosis in chimpanzees. Several other cooperative projects with outside investigators are underway including studies of primate hematology and immunology, antibody reactions in newborn chimpanzees, and chromosomes of Celebes black apes.

An attempt is being made to breed Talapoin monkeys which are resistant to tuberculosis and could yield valuable clues to resistance of this disease.

From April 1963 to June 1964, 19 papers by members of the Yerkes staff were published.

Wisconsin Regional Primate Research Center - University of Wisconsin

In January 1964, construction for the central Wisconsin Regional Primate Research Center was completed; the buildings were occupied soon thereafter, and officially dedicated in April. The Center is almost fully operational. An off-campus holding facility, now under construction, should be completed and in operation in June 1964. The Center's special research facilities include a nursery for the care of infant monkeys, an electron microscope laboratory, a surgical facility, a comparative learning research laboratory, behavioral testing rooms, a new photographic laboratory, and chemistry laboratories. With the additional space, all units plan expansion of their programs in mental retardation, physiology, experimental pathology, social psychology and psychology learning.

In the last year, 442 primates were used in various research projects at the Center.

Regional Primate Research Center - University of Washington

This center, now under construction, will be completed in October 1964. A major development during the past 18 months has been a service to provide scientific information on primate research to local, national and international biomedical research institutions. In the last ten months, 29 requests from this country and abroad were processed. One request was an emergency appeal for clinical data which would enable physicians and veterinarians to determine if a chimpanzee was the source of a serious, undiagnosed illness of its keeper, a request filled within the hour.

Among research projects in the Center are those on lipid metabolism and cardiovascular problems, pulmanary emphysema investigations, projects relating to eye diseases such as trachoma and myopia, and several neurological studies.

New cage designs for primates are being reviewed and some are undergoing tests.

New England Regional Primate Research Center - Harvard University

The final design plans and outline specifications have been approved for the Center. The Director and four core staff members have been appointed. Investigations have begun on the physiology of squirrel monkeys and the colonization of simian groups for future breeding purposes. Primates of several species have been used for the investigation and accumulation of comparative simian tissue.

Delta Regional Primate Research Center - Tulane University

Construction of the Center was begun in September 1963. Substantially complete are: the administration building, detached laboratory, isolation laboratory, service building, sewage disposal plant, and large field cage. The remaining buildings, consisting of main laboratory, large primate laboratory, steam plant, radiation field, will be completed by July 1964.

A staff of 54 has been employed: 12 investigators (8 Ph.D.'s and 4 M.D.'s), 10 technicians, 11 clerical workers, 10 animal caretakers, 12 maintenance men, and 8 shop men.

Research programs have begun in infectious diseases, with emphasis on the study of viral hepatitis. A behavioral sciences program has been initiated, consisting of field studies of primates in their native habitat and laboratory studies of neurophysiological correlates of behavior. Studies in environmental health involve investigations of Strontium-90 metabolism and its pathological consequences. Parasitological studies are directed toward an understanding of naturally occurring infections in recently imported animals. Cooperative studies are underway with a number of different institutions and investigators. Over 1,500 specimens of primate materials have been distributed upon request.

National Primate Conditioning Center - University of California, Davis

In May 1963, the Director, 21 investigators and associates transferred from Cincinnati to temporary quarters at Davis to continue work in the tuberculosis, malaria, carcinogenesis, and drug metabolism areas.

Plans for permanent facilities of the Center are completed and construction will begin in June 1964.

Now under development, is an experimental outdoor unit for testing the feasibility of housing various primate species in that climate.

Unique among the seven centers, the National Primate Conditioning Center has, as its main purpose, the study of primates themselves as biomedical research tools. It will provide a limited number of special primates to other institutions, but will not be a supply source to any great extent. The Center has a scientific staff of 44 which is expected to reach 200 when the Center is completed. The primate colony will number about 10,000.

In addition to the seven Primate Centers, the Branch administers eight grants which include studies on the maintenance and development of certain unusual, valuable strains of laboratory animals, and studies of laboratory animals in health and disease.

Problems

Because of the regional nature of the primate centers, special circumstances in their operations make some PHS policies and procedures which are applicable to research project grants inappropriate for the centers. For example, a special method of computing overhead costs and the award of indirect cost funds must be devised because the intent in this program is that the PHS pay all costs for the operation and maintenance of these regional centers. The Branch has prepared "A Guide to the Policies and Procedures Governing Grants Awarded for Operation of Regional Primate Research Centers" and has submitted it for official approval. The Guide suggests exceptions to policies governing research project grants.

The legal authority for the PHS to provide nonmatching funds for the construction of primate centers was terminated on June 30, 1962. There are, therefore, no nonmatching funds for new construction, but already evident is a potential need for additional construction. Because of the centers' regional and national orientation, it will be difficult for grantee institutions to provide matching funds for construction. There is evidence that this problem will become even more pressing in the future.

Future Objectives

It is planned to establish an Advisory Committee on Primate Research Centers to counsel the Branch on program development, to review applications for funds supplemental to base grant awards, to assist in the review of the centers' annual budget negotiations, and in the possible development of future primate centers.

In the past, DRG has been responsible for assisting the Surgeon General in certifying for the Indian government the need for rhesus monkeys for various biomedical research programs and drug companies in this country. Plans have now been completed for transferring this responsibility to the ARB, the logical focal point for research animal activities within the Public Health Service.

The ARB will continue its attempt to obtain more realistic review of animal resource applications. The philosophy of such programs is somewhat new and reviewing groups evaluating research projects from the viewpoint of scientific merit must become acquainted with the philosophy of this program. Thus, it will be a major task to orient all review groups concerned.

If funds are available, the ARB would include the establishment of two centers for intensive research in laboratory animal medicine; allow for the addition of project grants in this same field programmed so that the two centers and general research projects constitute a coordinated, integrated, planned attack; and to start a small highly selective training program to develop research veterinarians vitally needed in all large or medium-sized biomedical research centers.

Budget

The funds for the regional primate centers during this period increased from $5,120,000 in FY 1963 to $5,700,000 in FY 1964. Though no funds were approved for other animal resources programs, a total of $533,547 was obtained from other sources within the Division for these projects and $712,035 was provided by other NIH Institutes for grants this Branch administers.

GENERAL CLINICAL RESEARCH CENTERS BRANCH

Program Goals

The general clinical research center program provides a total facility which gives the environmental control necessary for valid scientific results in clinical research. In most hospitals, the wards with their primary commitment to patient care could not make available to the scientist research facilities he needs for such detailed, sophisticated studies. The general clinical research center provides this research facility, a discrete, fully equipped unit including laboratories.

Accomplishments

The growth of the program is illustrated in Table I. As of June 30, 1964 there were 959 beds in 78 centers in 65 institutions. Of these centers, 63, with 744 beds, are in operation in 30 states, the District of Columbia, and Puerto Rico. (A listing of the centers by state is appended to this section of the report.)

The sharp growth resulting in the establishment of 78 general clinical research centers in the four years of the program is now leveling off. As can be seen from Table I, new types of general centers, such as the premature center, the acute center, and the perinatal center, have increased and, although this area will continue to expand, it is not expected to constitute a large segment of the total program. New applications and supplements will continue and thoughtful staff work will ensure a continuing level of excellence.

In their annual reports for the period ending September 30, 1963, 56 centers reported 405 scientific publications, including 25 abstracts.

A few of the research accomplishments described in these papers are:

1. To reduce perinatal mortality and morbidity, the measurement of

twenty-four hour urinary estriol has been found to be a reliable index of placental function. By studying urinary estriol in pregnant diabetics, hypertensives, elderly primagravida, and women with histories of unexplained stillbirth, scientists identified by this method those patients who were developing placental insufficiency and those who could carry to term. (University of Pennsylvania)

2. By the use of drug immuno-suppression, prolonged survival of kidney homograft transplants has been possible. The longest survival is now over one year. (University of Colorado and the Medical College of Virginia)

3. By measuring the lactic dehydrogenase (LDH) and alkaline phophatase activity in the urine, it is possible to provide an accurate, sensitive, routine method for the detection of renal adenocarcinoma. (Peter Bent Brigham)

4. Ethyl p-chlorophenoxyisobutyrate (C.P.I.B.) has been found to reduce serum cholesterol, triglycerides, and the cholesterol-phospholipid ratio in man. It is non-toxic, easily administered and may hold promise in the treatment of atherosclerotic heart disease. (Montefiore Hospital, New York)

5. A technique has been developed for the quantitative measurement of coronary artery blood flow and studies have been combined with cine-angiographic visualization of the coronary arteries. This method of evaluating coronary flow has proved useful in selecting patients for surgery. (Johns Hopkins Hospital)

6. I^{131} labeled plasma insulin disappearance has been found useful as a guide to the management of Diabetes Mellitus. Those patients with the longest half-life for disappearance of labeled insulin (740 minutes) obtained optimal regulation on regular insulin. Those who showed a half-life in the range of 20-40 minutes were best regulated with mixtures of isophane and regular insulin. Those with an insulin half-life of less than 20 minutes were best regulated on isophane insulin alone. (University of Kansas)

7. By studying calcium balance in patients with osteoporosis after giving sodium fluoride, investigators found the fluoride created a positive calcium balance and thereby warrants further clinical trials as a therapeutic. (University of Washington)

8. Methotrexate, useful in a variety of cancers, has been studied and found to be retained in cells by being bound to the enzyme dihydrofolate reductase. (Yale University)

9. The D C defibrillator now in use as a therapeutic device in cardiac arrhythmias was developed and tested in a GCRC. (Peter Bent Brigham)

10. The delineation of various types of hyperlipemia and the therapies for each were reported from a GCRC. (University of Pennsylvania)

11. The regulation of ACTH secretion via a feedback mechanism with cortisone was shown to be not operative in stressed patients. Furthermore, lack of diurnal variation of ACTH secretion was thought to be a primary etiologic factor in Cushing's syndrome. (Vanderbilt University)

12. Ethacrynic acid is a new diuretic drug with a potency comparable to parenteral organo-mercurials able to produce diuresis in patients who were refractory to maximal doses of either thiazide or mercurial diuretics. (University of Pennsylvania)

The impact of the discrete general clinical research center on the grantee institution is well summarized by a center program director who said in his annual report:

"The general clinical research center serves as a model of clinical investigation for the total faculty, students and research fellows. Prior to opening of the Center, clinical research was available only on indigent wards or on private floors. Precision of study was not possible. The quality of facilities available and results obtained have stimulated interest in research in divisions of the Medical Center not previously involved with clinical investigation.

"The availability of these facilities has been of benefit in recruitment of faculty, house staff, and research fellows for the Medical Center. This in turn leads to continued improvement of scientific quality of investigation as new investigators and fellows in research training join the staff.

"The Center serves as the central area of clinical investigation for the Medical Center. An important influence exerted by the Center is in the increased number of interdisciplinary studies now in progress. Exchange of patients for study is frequent; one striking example was an obese diabetic patient who was studied under four protocols.

"The impact on the hospital nursing service is evident in the large number of requests for procedural information. Personnel from the Center are frequently asked to participate in regular hospital personnel conferences as sources of consultation and information.

"Social research in the hospital environment is in the formative stages and great efforts are being made to define this area. The interest generated has led to independent and collaborative social research studies both within and without the Clinical Research Center.

"Like the nursing section, the dietetic research section serves as an information source for the general hospital. Research dieticians played a primary role in planning the dietetic internship program initiated this year in a major University Hospital.

The international effects of the general clinical research center program are noted in a recent report of a U.S. cultural exchange delegated on Medical Education in the Soviet Union which states: "The USSR Ministry of Health has recently approved the planning and construction of 40 'central laboratories.' These will be attached to medical institutes and will be utilized for multidisciplinary clinical research. The organization and function of these laboratories appears to be comparable to those sponsored by the National Institutes of Health under the Clinical Research Centers program. Several Soviet medical educators informed the delegation that these laboratories will strengthen the role of scientific research in the teaching programs of the medical institutes."

Major Problems

Paramount among program problems continues to be the hospitalization policy. While this policy was evolving, a proposal for the separation of research and normal care on discrete centers was found to be conceptually unsound and was abandoned. Though less damaging to the discrete center program than the separation of research and normal care would have been, the proposed hospitalization reimbursement formula of average per diem-times-census appears to be applying certain pressures for quantity perhaps at a sacrifice of quality. The new hospitalization policy will require reasoned implementation by NIH staff who will be called upon to explain the background, flexibility, and intent of the NIH in supporting discrete clinical centers. Applying the principles of "per diem-times-census" as a method of hospitalization settlement retroactively, will require even great understanding, patience, and ingenuity. NIH staff will have to present a reasonable, cohesive policy which will support this important program and fulfill the exigencies of fiscal responsibility in dealing with Federal funds. No heavy-handed, unthinking beaureaucratic administration will suffice for either the grants settlement problems or future financial administration.

Future Objectives

For the next few years, the program will enter a period of steady growth during which a critical analysis will be made of existing centers. There are needs for new types of general centers which have so far been excluded from the program. One type is the general clinical research center for outpatients or for ambulatory patients not requiring all the services of the present type of clinical center, but nevertheless requiring multidisciplinary resources. Extending the scope of the general clinical research center program to include outpatients as a study population would be a rational expansion of program aims.

Another policy area to be evaluated is that of possible awards to new medical schools. Such awards would benefit these schools however; care must be exercised to see that the required minimum critical mass of clinical research competence is represented in the school. Missionary zeal must not overcome common sense. Such centers could be small initially and expand as the school developed. Clinical research competence should be judged in new schools, as elsewhere, on productivity and merit. Regular categorical project grants should be used in most cases, but where exceptions are found the program should respond flexibly but with precision.

Budget

From January 1963 to June 1964 the General Clinical Research Centers Branch reviewed 41 applications, of which 25 were new and 16 supplements. Of these applications, 28 were approved, 4 were deferred, and 9 were disapproved.

Funds available as well as funds awarded by fiscal year are shown in Table II. The awards in FY 1963 totaled $17.4 million. With an appropriation of $33.5 million for that year, a surplus of $16.1 million resulted, of which some $2.6 million was transferred to other parts of the Division.

This surplus can be attributed to three basic factors: 1) reduction of fund requirements under the October 1 common anniversary date mechanism; 2) slight overestimation of number of new awards; and 3) reduction of funds required for supplements. Approximately $7.7 million in unused funds resulted from the first factor because, under the October 1 common anniversary date provision initiated in FY 1962, new awards approved in FY 1962 carried through September 30, 1963 and averaged about 18 months each. Consequently, no continuation funds were required in FY 1963 on the 1962 awards. Approximately $5.6 million surplus is attributed to the second factor -- only 11 new awards were made. Savings totalling $2. 8 million in supplements represent the third element of the surplus.

In FY 1964, the situation altered considerably with less than one per cent of all the funds available in the program remaining unexpended.

The estimated[1/] activity and financial picture for FY 1964 is as follows:

	No. of Centers	(millions) Dollars
A. Funds Available		
Appropriation	...	$27.9
Less: Transfers & unprogrammed funds	...	.8
Net funds available	...	$27.1
B. Awards		
Continuations, requiring funds	56	$20.2
Continuations, not requiring funds until FY 1965*	11	.0
Supplements	(09)	.7
New awards	11	6.2
Total awards	78	$27.1

1/ Based on actual data through 5/17/64 and NARRC recommendations on 5/18/64

*Awarded in FY 1963

The President's Budget of $27,684,000 for FY 1965 appears to be adequate to support the following program:

Item	No. of Centers	Amount
Continuations, requiring funds	67	$23,900,000
Continuations, not requiring funds until FY 1966*	11	0
Supplements	(13)	1,284,000
New	5	2,500,000
Total	83	$27,684,000

*Awarded in FY 1964

Table 1

CUMULATIVE STATUS AND TYPES OF GENERAL CLINICAL RESEARCH CENTERS

FY 1960 - 1964

Type of Center	Cumulative Status of Centers				
	FY 1960	FY 1961	FY 1962	FY 1963	FY 1964
Adult [a]	8	31	43	48	55
Children's		1	8	13	16
Adult-Children's [b]			3	3	3
Premature			1	1	1
Acute			1	1	1
Chronic				1	1
Maternal-Child	—	—	—	—	1
Totals	8	32	56	67	78

a/ Adult Centers may also admit children.

b/ Consists of separate adult and children sections under one Program Director.

Table 2

BUDGETARY AND QUANTITATIVE DATA

FY 1960 - FY 1964

GENERAL CLINICAL RESEARCH CENTERS

FY	Number of Centers		Funds Budgeted 1/	Funds Awarded 1/
	New Awards	Cumulative Total		
1960	8	8	$ 3.0	$ 3.0
1961	24	32	8.0	8.0
1962	24	56	27.5	22.1
1963	11	67	33.5	17.4
1964	11	78	27.9	27.1
Totals	78	78	$99.9	$77.6

1/ In millions of dollars.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH FACILITIES AND RESOURCES
GENERAL CLINICAL RESEARCH CENTERS
STATUS REPORT

June 1, 1964

State	Institution & Program Director	Grant No.	No. Beds Approved	Beginning Date of Initial Award	Temporary Unit Activation Date	Temporary Unit No. Beds	Permanent Unit Activation Date	Permanent Unit No. Beds
Alabama								
	Univ. of Alabama Dr. C. K. Meador	FR-32	12	11/1/60			6/25/62	12
Arkansas								
	Univ. of Arkansas Dr. W. J. Flanigan	FR-49	12	5/1/61			11/1/61	12
California								
	Children's Hosp.-L.A. Dr. G. N. Donnell	FR-86	8	6/25/62			10/28/63	8
	Univ. of Calif.-S.F. Dr. P. H. Forsham	FR-79	15	5/1/62			8/1/63 1/1/64	10 15
	Univ. of Calif.-S.F. Dr. E. G. Biglieri	FR-83	9	6/1/62			2/24/64	9
	Univ. of So. Calif. Dr. D. H. Nelson	FR-43	15	5/1/60			4/11/61	10
	Stanford Univ.-Premature Dr. M. Klaus	FR-81	6	5/1/62			5/28/63	6
	Stanford Univ. Dr. J. W. Farquhar	FR-70	31	6/1/62	6/21/63 3/1/64 4/2/64 4/25/64	5 20 22 25		
Colorado								
	Univ. of Colorado Dr. D. Jenkins	FR-51	22	5/1/61	2/5/62	10		
	Univ. of Colorado (Child) Dr. Donough O'Brien	FR-69	6	1/1/62	3/12/62	4		
Connecticut								
	Yale Univ. Dr. J. W. Hollingsworth	FR-38	14	11/1/60	4/17/61	8		
	Yale Univ. (Child) Dr. C. D. Cook *	FR-125	6	6/1/63			9/16/63	6
District of Columbia								
	Georgetown Univ. Dr. G. E. Schreiner	FR-60	16	5/1/61			5/1/62	16
Florida								
	Univ. of Florida Dr. W. C. Thomas	FR-82	10	6/25/62			10/8/62	10
Georgia								
	Emory Univ. Dr. E. G. Herndon	FR-39	16	5/1/60			1/4/61 12/11/61	10 16
	Med. Col. of Georgia Dr. W. V. Greenberg	FR-61	10	5/1/61			2/26/62	10

* Effective 6/22/64

State	Institution & Program Director	Grant No.	No. Beds Approved	Beginning Date of Initial Award	Temporary Unit Activation Date	Temporary Unit No. Beds	Permanent Unit Activation Date	Permanent Unit No. Beds
Illinois								
	Children's Mem. Hosp.-Chicago Dr. O. C. Green	FR-199	6	6/1/64				
	Univ. of Chicago Dr. R. L. Landau	FR-55	29	5/1/61			8/10/61	29
	Univ. of Illinois Dr. M. M. Stanley	FR-45	9	1/1/62			7/18/63 9/13/63	8 9
	Northwestern Univ. Dr. F. del Greco	FR-48	14	5/1/61			1/2/62	14
Indiana								
	Univ. of Indiana Dr. W. P. Deiss, Jr.	FR-57	7	1/1/62			7/8/63	7
Iowa								
	State Univ. of Iowa Dr. W. A. Krehl	FR-59	20	5/1/61	12/14/61	8		
Kansas								
	Univ. of Kansas Dr. R. E. Bolinger	FR-67	10	1/1/62			4/19/63	10
Kentucky								
	Univ. of Kentucky Dr. W. W. Winternitz	FR-158	10	1/1/64				
Maryland								
	Johns Hopkins Univ. Dr. W. G. Walker	FR-35	21	5/1/60			8/1/60	21
	Johns Hopkins Univ. (Child) Dr. B. Childs	FR-52	8	5/1/61	10/14/61	6		
	Univ. of Maryland Dr. T. B. Conner	FR-33	10	11/1/60			12/11/62	10
Massachusetts								
	Boston City Hosp. (Child) Dr. R. Klein	FR-103	8	5/1/63			10/7/63	8
	Children's Hosp. Med.Ctr.-Boston Dr. W. F. Bernhard	FR-128	12	6/1/64				
	Harvard Med. School-P.B.B. Dr. G. W. Thorn	FR-31	24	11/1/60			10/16/61	24
	Harvard Med. School-B.C.H. Dr. S. H. Ingbar	FR-76	18	6/25/62	8/1/63	12		
	Tufts Univ. Dr. E. B. Astwood	FR-54	14	5/1/61			4/23/62	14
	Mass. Inst. of Tech. Dr. D. M. Watkin	FR-88	10	12/1/62				
Michigan								
	Univ. of Michigan Dr. A. B. French	FR-42	20	5/1/60			5/15/62	20
	Wayne State Univ. Dr. C. F. Whitten	FR-74	6	6/25/62	4/15/63	6		
Mississippi								
	Univ. of Mississippi Dr. J. D. Smith	FR-91	6(T*)	12/1/62	5/6/63	6		

* Temporary

State	Institution & Program Director	Grant No.	No. Beds Approved	Beginning Date of Initial Award	Temporary Unit Activation Date	Temporary Unit No. Beds	Permanent Unit Activation Date	Permanent Unit No. Beds
Missouri								
	(Washington Univ.-St. Louis	FR-36	15	5/1/60			10/10/60	15)
	(Washington Univ. (Child Portion) Dr. D. M. Kipnis	FR-36	8	7/1/62			7/18/63	8)
New Jersey								
	Seton Hall Col. of Med. & D. Dr. P. H. Henneman	FR-41	12	11/1/60	6/1/61	8	12/20/62	12
New York								
	Albany Med. Col. Dr. J. E. Kiley	FR-94	8	8/15/63				
	Albert Einstein Col. Dr. Q. B. Deming	FR-50	20	5/1/61			4/15/63	20
	Albert Einstein Col. (Acute) Dr. S. M. Levenson	FR-66	6	6/1/62				
	Cornell Univ. Dr. E. L. Becker	FR-47	20	11/1/60			4/16/62	20
	Mt. Sinai Hosp. Dr. S. Kupfer	FR-71	12	10/1/63	3/10/64	6		
	Montefiore Hosp. Dr. L. Hellman	FR-53	18	5/1/61	12/20/61	6	12/26/63	18
	(New York Univ.-Bellevue	FR-96	12	5/1/60	11/1/60	6	12/12/61	12)
	(New York Univ.-Bellevue (Child Dr. C. McEwen Portion)	FR-96	9	7/1/61			2/11/63	8)
	Rockefeller Inst. Dr. M. McCarty	FR-102	20	4/1/63			4/1/63	20
	Univ. of Rochester Dr. C. Waterhouse	FR-44	8(T*)	11/1/60	1/16/61	8		
	St. Univ. of N.Y. (Buffalo) Dr. S. J. Yaffe	FR-77	8	6/1/62			10/28/63	8
	St. Univ. of N.Y. (Syracuse) Dr. A. J. Schneider	FR-85	10	6/25/62	6/17/63	5		
North Carolina								
	Duke Univ. Dr. J. B. Sidbury, Jr.	FR-30	21	12/1/60	12/1/60	15	5/27/63	15
	Univ. of North Carolina Dr. W. Hollander, Jr.	FR-46	10-1 yr. 12-2 yr. 14-3 yr. 15-4 yr.	11/1/60	1/9/62	10		
Ohio								
	Children's Hosp.-Columbus Dr. J. F. Sotos	FR-78	6	6/25/62				
	Children's Hosp.-Cincinnati Dr. W. K. Schubert	FR-123	8	6/1/63			4/20/64	8
	Univ. of Cincinnati Dr. H. C. Knowles	FR-68	4(T*)	1/1/62	10/1/62	4		
	Ohio State Univ. Dr. G. J. Hamwi	FR-34	12	11/1/60			3/13/61	12
	Western Reserve Univ.(Perinatal) Dr. E. J. Quilligan Dr. R. Schwartz	FR-210	12	6/1/64				

* Temporary

State	Institution & Program Director	Grant No.	No. Beds Approved	Beginning Date of Initial Award	Temporary Unit Activation Date	Temporary Unit No. Beds	Permanent Unit Activation Date	Permanent Unit No. Beds
Ohio - continued								
	Univ. Hosp. of Cleveland Dr. M. Miller	FR-80	12	6/1/62			6/17/62 9/17/62 2/11/63	8 10 12
	Univ. Hosp.of Cleveland (Child) Dr. T. M. Teree	FR-87	4(T*)	1/1/63	4/17/63	4		
Oklahoma								
	Univ. of Oklahoma Dr. J. R. Seely	FR-62	10	1/1/62				
Pennsylvania								
	Jefferson Med. Col. Dr. L. G. Wesson, Jr.	FR-72	10	4/1/62			2/6/64	10
	Univ. of Pennsylvania Dr. L. W. Bluemle, Jr.	FR-40	12	5/1/60	11/23/60	5	2/20/62	10
	Philadelphia Gen. Hosp. Dr. D. J. Prockop	FR-107	8	4/1/63				
	Univ. of Pittsburgh Dr. J. B. Field	FR-56	14	5/1/61			4/25/62	14
	Children's Hosp.-Pittsburgh Dr. J. Egan	FR-84	6	6/1/62			1/8/63	6
	St. Christopher's Hosp. for Child. & Temple Univ. Dr. A. E. McElfresh	FR-75	8	1/1/63			1/30/63	8
Tennessee								
	Univ. of Tennessee Dr. I. F. Tullis	FR-211	14	6/1/64				
	Vanderbilt Univ. Dr. E. V. Newman	FR-95	21	11/1/60	3/1/61	10	10/17/62	21
Texas								
	Baylor Univ. (Chronic) Dr. W. A. Spencer	FR-129	6	6/1/63			9/4/63	6
	Baylor Univ. (Child) Dr. G. W. Clayton	FR-188	6	1/1/64				
	Baylor Univ. (Meth. Hosp) Dr. H. Brown	FR-134	6	12/30/63				
	Univ. of Texas-Galveston Dr. W. C. Levin	FR-73	10	6/1/62			6/24/63	10
Utah								
	Univ. of Utah Dr. F. H. Tyler	FR-64	20	4/1/64				
Vermont								
	Univ. of Vermont Dr. J. H. Bryant	FR-109	6	4/1/63	1/6/64	6		
Virginia								
	Med. Col. of Virginia Dr. W. R. Harlan, Jr.	FR-65	9	1/1/62			11/9/62	9
Washington								
	(Univ. of Washington	FR-37	12	5/1/60	7/19/60	12)		
	(Univ. of Washington(Child.Portion) Dr. F. C. Wood, Jr.	FR-37	4	5/1/62	10/1/62	4)		
	Univ. of Washington-King Cty. Dr. J. T. Dowling	FR-133	8	6/1/64				

* Temporary

State	Institution & Program Director	Grant No.	No. Beds Approved	Beginning Date of Initial Award	Temporary Unit Activation Date	Temporary Unit No. Beds	Permanent Unit Activation Date	Permanent Unit No. Beds
Wisconsin								
	Marquette Univ. Dr. E. J. Lennon	FR-58	10	5/1/61			1/16/62	10
Puerto Rico								
	Univ. of Puerto Rico Dr. A. A. Cintron-Rivera	FR-63	12	1/1/62			9/6/63 9/20/63	6 12

GENERAL RESEARCH SUPPORT BRANCH

Program Goals

The General Research Support program provides broad support for the professional health research and research training institution. It is a complementary support which permits the institution great flexibility in determining and developing those areas which contribute most effectively to its total research and research training capability. Funds for the General Research Support program come from each of the Institutes of NIH.

The goals of the GRS program are best served when institutions employ these grants for:

1. Support of Research: to introduce new research activities to an institution; to support collaboration among relatively remote research disciplines where project type research is difficult to formulate; to launch pilot projects and support research activities previously supported through small grants programs; to support the exploration of promising ideas that require further development before being submitted for research project support in national competition; to defray unanticipated expenses in established research projects.

2. Support of Personnel: to provide stable salary support for key research personnel; to pay salaries, stipends, tuition and fees for persons engaged in health research training; to provide funds for travel, conferences, and scientific communications; to support salaries of professional and technical personnel for their direct contributions to health research and research training.

3. Support of Resources: to support central research resources essential to the general support of many health-related research and research training activities within the institution; to provide general purpose research equipment that serves the needs of multiple projects and programs; to maintain essential central resources for consumable supplies and for both special and general purpose research services.

4. Special Uses: to support research grants for less than $2000 in one year; supplemental grants to research projects to cover institution-wide salary increases during an active grant year; and grants for student part-time and post-sophomore fellowship programs.

Accomplishments

In 1963, the GRS Branch provided continuity of support for the 153 health professional schools automatically eligible and which had received awards at the outset of the program in 1962. With broadening of categories to include other types of institutions, 111 additional institutions became eligible in 1963. In 1964, the number of grantee institutions remained fairly constant, a little more than 260.

In the past 18 months, several extensive reports on the use of GRS awards were prepared for the National Advisory Health Council. The reports analyzed the experiences of the first year of the GRS program, but included as

well, data from grant applications for the first three years of the program.

The reports showed that, in general, institutions expended slightly more than half their awards during the first grant year, indicating that this initial period was used more for planning than spending; the liberal GRS carry-over policy permitted them an increased amount of money for general research support during the second grant year. Despite this self-imposed check on spending, more than 2000 professional and technical personnel received whole or partial salary support from the grants. Thirty-eight per cent of this expenditure paid salaries to persons of professorial rank, 40 per cent to other professional workers, and the remainder to research technicians. More than 2000 persons received research training. Over 1500 research projects were supported, of which more than 1100 were new. More than two-thirds of the latter were in the "under $2000" category of small grants.

In the central research resources category, nearly half the money was spent on animal facilities, reflecting a long-standing, institutional need not readily met through the individual research project grants. Other central research resources supported by GRS grants included specialized library research resources, radiological control, electronic, mechanical and glass blowing shops, research photography, and statistical processing.

The program made possible the recruitment of scores of new research personnel in grantee institutions. Many of these recruits became department chairmen or filled other highly responsible positions. More than twenty new departments and dozens of new research laboratories were established with GRS funds. In short, it is evident that the general purposes for which this program was originally established <u>are</u> being met.

The GRS program was accelerated by six months to accommodate two complete grant application and payment sequences within a single calendar year. This enables the Branch to make awards at the beginning of each new grant year.

A revision of the <u>GRS Policy and Information Statement</u> based upon operating experiences of the first two years clarified certain policies and procedures and enhanced understanding between the NIH and grantee institutions.

Other changes during the reporting period that improved GRS grants management:

Institutions are now required to name a senior, responsible individual of professional, scientific stature as the person responsible for the institutional utilization of a GRS grant.

Wherever full accreditation is not established, the NIH staff and the National Advisory Health Council review institutional status on a case-by-case basis. The Council and staff plan to review the several aspects of accreditation to the extent that this matter affects Branch policies.

To aid the staff and Council in the evaluation of individual applicant institutions, the staff now invites marginal institutions to submit additional information respecting their <u>total health-related research activities</u>.

Major Problems

Because of an "interim regulation" imposed by the Bureau of the Budget, the GRS program to date has been unable to extend its awards to university components other than the health professional schools. A vital segment, important in size and superb in quality, of the national health research program has thus been excluded. These university components receive more than 20 percent of all NIH research project awards; they are in the vanguard of the biological, physical, and behavioral sciences. Furthermore, universities are the source of doctorates in science destined to be of even increased importance to the future contributions of teaching and research, not only in universities but in the health professional schools as well, due to the lag of medical manpower training through lack of teaching facilities.

If the GRS Branch were authorized to provide grants to these university components, the grants could cover in one award to a university all appropriate components other than those which now receive support through the GRS program. Based on a formula, the award would be comparable to that of the National Science Foundation for its Institutional Grants for Science program. Entitlement would be determined solely on the basis of the total of appropriate NIH grants. Thus, the application would not include for entitlement other Federal or non-Federal health research expenditures. In view of these distinctions, this grant might appropriately be identified as a university health research support grant.

If authority is given to provide university health research support grants, all the major public or nonprofit institutions heavily engaged in health-related research will be included in the program.

Future Objectives

Because of the increasing concern over the extent to which recipient institutions, particularly those marginally eligible for GRS grants, have been meeting their obligations in the support of excellent research and training, and because of the related contingency of the defense of the FY 1966 GRS budget and succeeding budgets for the next few years, it has been established by unanimous staff and National Advisory Health Council agreement that it is essential to undertake immediately a preliminary program evaluation. It will primarily be concerned with evaluating low-ranking or marginal institutions supported by the program. This evaluation is planned for completion by about November 1, 1964, for reporting soon thereafter to the National Advisory Health Council and to the Director, NIH. The timing is essential to justify certain aspects of the GRS budget for 1966. This necessitates accelerating the long-range program evaluation originally planned for implementation during calendar year 1965.

A preliminary program evaluation, approved and already being planned, involves detailed, selected institution-by-institution as well as bulk program analysis to include subjective as well as factual reporting. It also involves institutional site visiting to more than 20 institutions, mainly marginal ones, although others will be included. The site visits will include three schools of dentistry, two schools of medicine, four hospitals, two research foundations, one research institute, and one State Department of public health.

A longer-range program evaluation will be undertaken according to the original schedule and will make use of criteria established earlier.

Authorization has been granted to establish a GRS Committee to review new applications and evaluate information provided through institutional reports and institutional site visits. Evaluations by this Committee will strengthen staff practices and procedures and provide guidance on general policies recommended by the National Advisory Health Council.

Budget

In relation to the total appropriated for NIH research project grants the percentage to General Research Support for the three years was:

FY 1962--5.6%, 1963--7.0%, 1964--7.3%.

In 1963, $30,000,000 was provided in the GRS budget. This permitted continuing support to the first 153 institutions which had received awards in 1962. These institutions were given the same proration in 1963 as in 1962. On advice of the National Advisory Health Council, however, the 111 new institutions were given a lesser proration amounting to about one-third of that available to the previous grantees.

In 1964, the $35,000,000 budget permitted making awards to all eligible institutions with a uniform proration increased slightly over that for 1962 and 1963.

HEALTH RESEARCH FACILITIES BRANCH

Program Goals

The Health Research Facilities program provides grants for construction, large-scale renovation, and equipment which raise the quality and productivity of biomedical research by improving the environment in which it takes place.

Under Title VII A of the Public Health Service Act, awards are made up to 50 per cent of the total cost of health-related facilities and equipment. Under Title VII D (the mental retardation research centers program authorized by the Congress in 1963), awards may be made up to 75 per cent of the costs of the mental retardation research portion of the centers.

Active since 1956, the Title VII A program responsibilities were broadened in 1963 by P.L. 88-129, the Health Professions Teaching Facilities Act under which facilities will be constructed as multipurpose buildings, requiring coordination of administrative action on the review and approval of requests for teaching and research space. Furthermore, during the past 18 months there has been an increased emphasis on support of facilities which must be provided on university and institutional compuses to house adequately research programs of importance to various components of the Public Health Service, such as the National Institutes of Health and the Divisions of

Environmental Health and Community Health in the Bureau of State Services. Thus, while it has long been known that, beyond a certain point, an institution cannot effectively use additional research funds unless additional physical facilities also are available, it is only recently that this problem has been viewed in its proper perspective. As a consequence, the Branch staff has spent considerable time coordinating Council approved facilities requests with the priority needs of the several PHS Divisions and NIH Institutes.

Accomplishments

Under the Title VII A program, eligible institutions are required to provide at least 50 per cent of the cost of the proposed facility from non-federal sources. In the eight years the program has been operating, 391 institutions have been awarded 1170 grants totalling $279,997,693 for the construction of facilities which are expected to cost approximately $1,377,583,261, of which the health-related area cost will be $734,526,540.

The program continued to emphasize assistance to broad institutional developments in health-related research facilities. Consequently, it has been possible during the past 18 months to lay the groundwork for new research centers, many of which are already under contract and will become operational in the next 18 to 24 months.

Major Problems

It has not been possible to activate all projects recommended for awards by the National Advisory Council on Health Research Facilities. As of June 30, 1964, approved, unpaid projects totaled 85, and would require an additional $33,760,239 to fund. Furthermore, passage of P.L. 88-129, already mentioned, resulted in submission of formal intentions to submit future applications to a new record high at $63,632,860. Based on past experience, these applications will result, after review, in approved requests of an additional $19,089,858.

Future Objectives

The Mental Retardation Research Centers Program was in the organizational stage during the last two months of 1963. Preliminary review was given to two applications for comprehensive, substantial research centers with the expectation that construction grants could be made during calendar year 1964.

It is understandable that, due to their inherent multidisciplinary character and multipurpose nature, considerable negotiation is necessary before actual activation of the grants. It is anticipated that grants for as many as eight such centers may be awarded during the four-year period authorized for this program.

SPECIAL RESEARCH RESOURCES BRANCH

Program Goals

During the 18 months covered by this report, the goals of the Special Research Resources Branch have been: (1) to establish and expand specialized, institutional resources which meet a well-defined, demonstrated need within an institution, region of the country, or field of science; and (2) to extend the program into new areas of biomedical sciences as unmet needs become apparent.

Special attention has been given to present and future needs of health research institutions, to current, evolving patterns of scientific development in physical and medical sciences, particularly the interdisciplinary aspects, and to a realistic evaluation of the ways by which Divisional program goals can be achieved within Public Health Service policies and available funds.

The Special Research Resources Branch has attempted to provide a balance between resources characterized as physical-science, or hardward-oriented, and those designed to serve more biologically-oriented needs. Examples of the former are computer and data processing, biomedical computer technology, biomedical engineering and bioinstrumentation, and proposed centers in biomathematics and biostatistics. The second type of resources includes an enzyme center, the American Type Culture Collection which collects, stores, and distributes to scientists cultures of living materials, and proposed critically needed resources for the support of research in analytical biochemistry, molecular biology, and electron microscopy.

Accomplishments

Some accomplishments of the Special Research Resources Branch during the past 18 months are:

1. Extended the initially circumscribed program from one which was hardware- and equipment-oriented into a balanced program for the support of research to meet multidisciplinary, multicategorical needs.

2. Established a Special Research Resources Branch Scientific Advisory Committee to advise staff on broad policies, program objectives, and national needs. This Committee is composed of experts in disciplines and fields of science relevant to the goals of the Branch.

3. Established cooperative relations with other government agencies, specifically NSF, NASA and AEC, for reviewing and supporting collaboratively large-scale programs for special research resources.

4. Prepared an annual progress report form for grantees to be used by Branch staff to assess the centers' activities and to negotiate award levels for subsequent grant periods.

5. Formulated a fee-for-service policy and discussed it with 27 center directors and institutional representives preparatory to its adoption as firm NIH policy for these centers.

6. Designed mechanisms and provided support for the continued develop-

ment, the large-scale field testing, and evaluation of the versatile, inexpensive, laboratory-oriented LINC (Laboratory Instrument Computer) computer.

7. Established by contract the first PHS-supported Regional Enzyme and Biopolymer Resource to make available to investigators selected research materials unavailable commercially.

8. Developed the Division's program goals and objectives in the area of biomedical communication sciences, and implemented them with a grant and contract program for selected scientific and technical information resources for investigators, institutions, and non-profit research organizations.

The Branch's program has been changed and improved primarily by the application of the concept that a special research resource is one which provides support for a wide spectrum of multidisciplinary and multicategorical research resource centers. Another improvement is the establishment of a Branch Scientific Advisory Committee to review the Branch's overall goals and objectives and to recommend ways in which policies may be formulated and implemented to secure maximal impact upon the course of medical sciences. Finally, the grants management, fiscal accountability, and grantee reporting systems have been improved and strengthened.

The truly significant contributions of the program are, of course, those made by the grantees and contractors who have received support from the Branch. With the many centers now receiving such support, it is possible to point to several general contributions to the biomedical sciences accomplished through this program.

In computation and data processing, special resources progress reports and on-site evaluations indicate that each institution with such a resource has improved significantly the quality and quantity of its biomedical research program because of the use of biomathematical techniques in experimental design, data reduction, and correlation and analysis of results. These special research resources are focal points in institutions for the dissemination of information about sophisticated computational techniques through seminars, short courses, and intra-resource training. Additional improvements result from the establishment within the centers of dynamic research programs in fields such as biomathematics and computer system design, particularly as applied to the recording and analysis of experimental laboratory analog data. Increasingly, biomedical investigators are learning to apply mathematical theories and techniques to their own research problems, thereby transforming some of the more descriptive areas of medical research into exact sciences. Neurophysiology, cardiovascular dynamics and physiology, electroencephalography, electrocardiography, biochemical kinetics, molecular biology, protein and macromolecular structure determination, epidemiology and biostatistics, medical diagnosis and others are being explored with rewarding results.

The special research resources program in biomedical engineering provides support for investigators who apply principles and tools of engineering sciences to complex problems of biology and medicine. For example, scientists are investigating ways of applying new developments in the field of ultrasonics to

the detection, recording, and analysis of patterns of blood flow solely by means of external transducers. Other research areas include investigations of eye movements and the use of specially designed recording devices to detect rapidly and sensitively, physiological activities and malfunctions; and the development of electronic and optical devices for observing and recording minute nerve cell impulses and electrical potentials from various parts of the brain and nervous system.

At the recently established New England Regional Enzyme and Biopolymer Resource, investigators are working on the isolation and production of specialized biochemical materials from human tissues and other sources for distribution to investigators. Only materials unavailable from any commercial source and those which meet the exacting scrutiny of an outstanding scientific advisory board, responsible for evaluating the investigator's request and his need for the material, are considered for preparation.

In the field of scientific and technical information resources, or biomedical communication centers, support has been given to the Science Information Exchange, to the Documentation Research Institute at Western Reserve University, and for studies on information retrieval systems and man-machine interfaces at Washington University and the University of Pittsburgh.

In still another facet of the Branch program, funds have been provided to the American Type Culture Collection to support this unique organization in its program of collection, storage, classification and distribution of pure cultures of bacteria, viruses, mammalian cells and other selected living organisms and materials needed by biomedical scientists. Serving the entire national community of biomedical investigators, this organization is a unique central repository for the basic materials and test systems of several sciences.

Another significant contribution through Branch support, is the successful development, field testing, and distribution to the scientific and computer technology community of the results of the LINC development program. A portable, ingeniously designed and versatile computer, it has been tested for almost a year in various biomedical research programs in the laboratories of 12 biomedical scientists. Investigations include cardiovascular physiology, learning behavior, and the formulation and testing of mathematical principles as applied to complex biological problems. This computer, for the first time, brings to the biomedical scientist the capability of recording and analyzing data, and indeed of controlling the course of an experiment while it is proceeding. Relatively inexpensive, the LINC can be adapted readily to particular experimental requirements in many ways, even by medical investigators untrained in computer techniques. The impact of this development on the future course of biomedical research is expected to be significant. It is already of great interest to the scientific community.

Major Problems

The major current problems of the program are either policy or operational.

Policy problems requiring further consideration include:

(1) a determination of the most effective means for introducing into institutional resource centers the formulated fee-for-service policy, and an assessment of what problems and impact this may have for each particular resource. In the course of a program re-evaluation, it became clear that it is desirable, whenever feasible, to introduce a fee-for-service policy into the operations of a center, so the center will not be limited in providing assistance to biomedical investigators who wish to use its resources. At the same time, the scientific review of each project will provide the Branch with the assurance that each project which receives assistance has scientific merit.

(2) the general question of the advantages and disadvantages in establishing regional or institutional resources. There is a need to establish criteria for determining conditions best suited for establishing a regional resource, and effective mechanisms for maintaining effective links between the regional resource and each of its several participating units.

(3) an executive determination is crucial now as to the extent to which and when it may be possible for a special research resource to include grants now termed "departmental, equipment or renovation," and under what conditions administrative or scientific groups at or below the departmental level should be considered eligible for support of this type of facility. There is yet no recognized NIH definition as to what constitutes a special research resource.

Of operational problems, the major one in the Branch continues to be lack of professional staff. Inadequate salary levels and unrealistic rigid Civil Service personnel classification requirements have made it impossible over the last two years to recruit able professional staff in computer management and biomedical engineering. The Civil Service classification system is sadly out of date in the face of the burgeoning new fields of computerized data processing and the information sciences; personnel of consequence in these fields have no appropriate representation in present Civil Service classification schemes. Consequently, there have been critical, detrimental delays in meeting the burgeoning needs for resources in these areas. Insufficient manpower has made it difficult to administer this complex, expanding program with the prudence necessary for these substantial investments of public funds.

Another operational problem has been the restriction on allowable research grant expenditures for renovation costs which may be incurred in establishing or expanding these large institutional centers. The present ceiling of $50,000 per project is often totally inadequate. In some instances, significantly larger amounts are necessary for renovation if the resource is to engage in a program suited to the number of its biomedical investigators and the scope of the research environment. With the establishment of the Office of Architecture and Engineering within the Division, it now is possible for the Branch to obtain expert technical advice and guidance on renovation requests. For maximum operating efficiency, however, it is essential that the present ceiling on renovations be removed.

Future Objectives

Future objectives in operations include: (1) establishment of the fee-for-service procedure in line with policy on an institution by institution basis in a phased, incremental fashion; (2) consideration of a more extensive use of contracts for the establishment of large resource centers, particularly where some measure of direction may be appropriate in initial stages; (3) recruitment of qualified professional staff to administer the present program and to forward the objectives of the program in a rational and effective manner; (4) continuation of close cooperation and discussions with the other NIH Institutes and the Division of Research Grants leading to the formulation of guidelines that will be the basis for clear-cut determination of assignment of applications to the Branch; (5) more effective and closer collaboration with executive officials, directors of research, and investigators at institutions in developing their ideas for resource centers and to assist in making such centers even more effective to the widest possible community of scientists.

For overall program policy, Branch staff will seek guidance from the Scientific Advisory Committee and the National Advisory Research Resources Committee especially on matters concerning long range program goals, national needs for biomedical resources, and ways in which interagency cooperative efforts may be used to achieve such goals.

Budget

Table I contains information on total funds available for grants and collaborative studies, and the estimated total amounts within each of these categories which have been approved for payment during the period January 1, 1963 through June 30, 1964. In the grant category, the total number of each type of application (new, competing continuation, etc.) have been tabulated; for the collaborative studies category, the individual programs have been identified.

In Table II, data show the total number of applications received, together with amounts requested, and the recommendations and amounts approved by the National Advisory Research Resources Committee during the period January 1, 1963 through June 30, 1964.

A total of 62* applications was received for a total requested amount of $17,054,712*. Following review of the applications by scientific review boards and the National Advisory Research Resources Committee, 38* applications were recommended for approval for a total amount of $7,064,187*; 18 applications were recommended for disapproval, and 6 for deferral.

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* Three additional applications (2 competing continuations and 1 supplement) were submitted and approved in the total amount of $438,947 but will not be awarded until FY 1965.

The total amount of dollars approved by the National Advisory Research Resources Committee ($7,064,187) and the total amount of dollars actually awarded ($6,721,046) following staff negotiation with each resource director and his institution resulted in a return to program of $343,141 by the Division. These so-called "savings" result primarily from a careful determination of how the staff and equipment of centers are phased into the resource operation; there was no attendant reduction in program capability or productivity.

TABLE 1

TOTAL AWARDS AND FUNDS AVAILABLE

January 1, 1963 - June 30, 1964

Special Research Resources Branch

	AWARDS*	AVAILABLE
Grant Funds		$9,870,511
New	$6,296,972	
Competing Continuations	300,896	
Non-Competing Continuations	2,451,625	
Supplements	763,963	
Total	$9,813,456	
Estimated Balance		$57,055
Collaborative Studies		$1,363,900
New England Enzyme and Biopolymer Resource at Tufts University	$644,900	
New England Center for Computer Technology and Research in the Biomedical Sciences	315,000	
Follow-up Agency	104,000	
Science Information Exchange	300,000**	
Total	$1,363,900	
Balance, Collaborative Studies		-0-

* All data are actual awards except for the new applications which are estimates of the nine approvals at the May 1964 meeting of The National Advisory Research Resources Committee and currently under negotiation.

** Transferred to NSF in FY 1964.

Table II

SPECIAL RESEARCH RESOURCES BRANCH

Council Review in Total Amounts*
January 1, 1963 - June 30, 1964

COUNCILS and Years	TOTAL REQUESTED No.	TOTAL REQUESTED Amount	TOTAL APPROVED No.	TOTAL APPROVED Amount	TOTAL AWARDED No.	TOTAL AWARDED Amount	TOTAL SAVINGS	TOTAL DEFERRED No.	TOTAL DEFERRED Amount	TOTAL DISAPPROVAL No.	TOTAL DISAPPROVAL Amount
New:											
March 1963	5	$1,254,701	2	$230,467	2	$267,590	$ -37,123	1	$410,680	2	$594,100
May 1963	17	5,774,941	12	4,232,639	12	3,540,810	691,829	1	573,114	4	806,851
Nov. 1963	15	5,333,025	7	899,020	7	1,136,914	-237,894	4	3,341,668	4	725,337
March 1964	1	315,611	1	315,611	1	181,308	134,303	-	-	-	-
May 1964	16	3,486,542	12	1,048,326	12	1,279,989	-231,663	-	-	4	1,529,701
Total New:	54	16,164,820	34	6,726,063	34	6,406,611	319,452+	6	4,325,462	14	3,655,989
Competing Continuations:											
May 1963	1	19,125	1	10,440	1	10,440	-	-	-	-	-
March 1964	0**	0**	0**	0**	-	-	-	-	-	-	-
May 1964	1**	47,208**	0**	0**	-	-	-	-	-	1	47,208
Total Competing Continuations:	2**	66,333**	1**	10,440**	1	10,440	-	-	-	1	47,208
Supplements:											
March 1963	1	56,267	1	56,267	1	40,918	15,349	-	-	-	-
Nov. 1963	2	240,916	-	-	-	-	-	-	-	2	240,916
March 1964	1	56,640	1	56,640	1	48,300	8,340	-	-	-	-
May 1964	2**	469,736**	1**	214,777**	1**	214,777	-	-	-	1	254,959
Total Supplements:	6**	823,559**	3**	327,684**	3	303,995	23,689	-	-	3	495,875
Grand Total	62**	$17,054,712**	38**	$7,064,187**	38	$6,721,046	$343,141**+	6	$4,325,462	18	$4,199,072

* All TOTAL amounts include direct and indirect cost amounts.

\+ This amount represents the NIH (DRFR-SRRB) savings on approved amounts after each of the 34 new grants were prorated to meet the PHS-established common anniversary date of October 1.

** Three additional applications (two competing continuations and one supplement) were submitted and approved in the total amount of $438,947, but will not be awarded until FY 1965.

CONCLUSION

Facing the Division in the immediate future are two major problems. The first is the exigency of long-range program planning for resources organized on a regional or national basis. Strong pressure has been exerted on the Division by the Director and by the Senate (Senate Report No. 383, page 39) to undertake such long-term planning and to incorporate this function as an integral part of the general Division activity.

The second major problem is the establishment of a grants management framework which encompasses modern financial management accounting principals, and the recruitment into key positions of management personnel with certified public accountancy backgrounds (or equivalent). Grants management including expert financial administration must at all times be responsive to the Divisional program needs and decisions.

Annual Report of Program Activities
Division of Research Grants
January 1963 through June 1964

Summary Statement

During the 18-month period covered by this report, the Division of Research Grants continued to coordinate the development of policies and procedures in Public Health Service grant administration and to provide principal scientific and technical review of grant and award applications.

The workload of processing and reviewing applications for extramural support has increased with the expansion of DRG's responsibilities to include extramural programs of the Community Health and Environmental Health Divisions of the Bureau of State Services. In fiscal year 1963, 24,994 grants and awards were made amounting to $650,759,657, compared to 23,747 totaling $571 million in fiscal year 1962.

Expansion and reorganization of administrative staff in the Division's Research Grants Review Branch and the Career Development Review Branch were necessary to strengthen operating functions involved in the processing and review of the various types of applications. To review and to insure competency in new and expanding areas of research, the Division created five new study sections, bringing the total to 51, and one new fellowship review panel for a total of 13. In addition to reviewing applications, the study sections were active in arranging conferences to stimulate research in unexplored or neglected areas. Some examples of the conferences that have broadened the research horizon are those on 1) evaluation and mechanism of drug toxicity; 2) recruitment of basic science students into fields of environmental research; 3) stimulation of clinically oriented research in bacteriology; 4) establishment of a national pituitary gland agency; and 5) stimulation of research in dental pulp and salivary glands. In several instances the exchange of information resulting from these conferences has led to publication. The recommendations of one study section resulted in the establishment of a visiting scientist program to accelerate an exchange of research information in the field of neuroanatomy.

The need for a more systematic approach to the management of grant programs led to the codification of PHS policies and regulations published as the Grants Manual in January 1963. A first revision was published and went into effect April 1, 1964.

Preceded by orientation seminars for PHS grants administration staff, regional meetings of grantee institutions were arranged by DRG to brief personnel on new grants administration procedures and supplement the information in the revised Manual. These meetings facilitated an exchange of views with local administrators, faculty members, public information officers and others concerned.

The DRG Newsletter was initiated as an administrative publication in February 1964 to augment the general effort toward strengthening communications

between PHS research grant administrators and grantees. The Newsletter will be published periodically to provide information on grant and award procedures, extramural program developments, and staff changes.

Dr. Eugene A. Confrey was appointed Chief of the Division in June 1963, upon the retirement of Dr. Dale R. Lindsay, who had served as Chief since 1960. Dr. Stephen P. Hatchett, former Chief of the Career Development Review Branch, was named Deputy Chief of DRG early in 1964. In recognition of his service and leadership in the Career Development Review Branch, Dr. Hatchett received the DHEW Superior Service Award in April 1963 and, at the time of his retirement, Dr. Lindsay was awarded the PHS Commissioned Officer Meritorious Service Medal.

OFFICE OF THE CHIEF

To meet the need for expanding activities in scientific evaluation, technical communications, analyses of extramural programs, statistical interpretations of grant support, and staff training and orientation, a major reorganization took place in the Office of the Chief.

Three new posts of Associate Chief were created and filled. Mr. Peyton Stapp was appointed Associate Chief for Analysis and Statistics; Dr. Arley T. Bever, Associate Chief for Research Analysis and Evaluation; and Dr. J. Palmer Saunders, former Chief of the Research Grants Review Branch was appointed Associate Chief for Scientific Review and Development.

Other key personnel appointments in the Division were Dr. Willis R. Boss, replacing Dr. Hatchett as Chief of the Career Development Review Branch; Dr. James Haggerty replacing Dr. Saunders as Chief of the Research Grants Review Branch; and Mr. Guerry R. Smith as Chief of the Grants Management Branch.

Since early September 1963, the Office of the Chief, DRG, has worked in close coordination with the Office of the Director, NIH, in the development of a study to increase the facility of research grants management. The major objectives of this study are the enhancement of scientific productivity of PHS-supported projects and an easing of the administrative workload.

The study has been directed toward increasing the role of the grantee institution in its project fiscal management, particularly with regard to items of budgetary change or expenditures which currently, according to Grants Manual procedures, require prior approval from the granting agency.

The first phase of the study, completed in January 1964, led to the conclusion that management of most of the "prior approval" items by the grantee was both desirable and feasible. The second phase, starting in February and ending in June 1964, considered the matters of the essential administrative structure in grantee institutions and the management procedural changes that might be necessary to implement a change in locus of "prior approval" authority for specific project expenditures. Particular attention was given to the means of bringing scientific judgment to bear on project management issues between the review periods of PHS advisory board and staff for initial or annual awards.

The second phase of the study has led naturally into a third, in which a small group of grantee institutions will work cooperatively with the PHS in an operational trial of the proposed procedural changes. The administrative mechanism for this trial is currently under development. Tentatively, the operational pilot study is scheduled to begin in the early fall of 1964.

Office of Associate Chief for Scientific Review and Development

The continued growth and increasing complexity of the DRG scientific review function as it relates to the total PHS extramural program has led to the need for a new focus of scientific responsibility within the Office of the Chief.

The newly-created Office of the Associate Chief for Scientific Review and Development has a primary responsibility for assessing the quality, efficiency and adequacy of the scientific and technical review function of the PHS. The purpose of this continuing assessment is to maintain a high standard of review of applications for all PHS extramural programs and to project future needs of the review mechanism, as for example, the impending emphasis that may be given to programmed research.

As an increasing number of extramural scientists derive support from other Federal agencies in areas of mutual interest, this office will provide a focal point for more effective liaison with the directors of the research programs of other agencies, both Federal and private, such as the National Science Foundation, Office of Naval Research, Atomic Energy Commission, the National Research Council, the American Cancer Society and American Heart Association.

In conjunction with the Chief and the Deputy Chief of the Division, and other professional staff advisors, the Associate Chief helps formulate recommendations for overall policies relating to grant activities, including the determination of ways and means by which these programs can best meet research needs at the national level, the range and latitude in which grantees conduct their programs, etc. He is also a principal adviser to the PHS bureau chiefs on appropriate review mechanisms in their adequacy to meet the program responsibilities of the Service, many of which originate through Congressional directives.

As a key informational source on the research grant and award activities throughout the Service, the Associate Chief explains in person or through correspondence the nature, scope, aims and opportunities of PHS programs to scientists as well as voluntary and private granting agencies, universities and medical schools. He makes use of these opportunities to provide information on policies governing grants and awards as well as to clarify the scientific review and administrative procedures involved. His position enables him to promote and explain the purpose and objectives of the PHS programs, to gather data and information concerning the policies and objectives of other agencies engaged in subsidizing research, and to exchange similar information for the purpose of determining areas of grants programs which may require adjustment in policies and objectives.

Office of Associate Chief for Analysis and Statistics

An office of Associate Chief for Analysis and Statistics was established to intensify the DRG effort in carrying out analytical studies of NIH programs and to improve the presentation of statistical data reflecting these programs. The effective development of such analytical studies are entirely dependent on the availability of adequate, accurate, and up-to-date information about the various programs. The primary effort of this office during its first year has, therefore, been directed toward the development and perfecting of the data processing activity. This emphasis will probably continue for another year until effective integration of the central record-keeping activity and the administrative processing of the extramural program documents can be accomplished. During this period of development the Associate Chief has also served as acting chief of the Statistics and Analysis Branch of DRG.

During the first year, tentative work has been begun towards integrating this central record, with its automated features, into the records maintained by the Institutes/Divisions for their program analysis and planning purposes. The key to this integration is believed to lie in the scientific classifications maintained by the Institutes/Divisions for their program guidance.

The accomplishment of overall integration involves an analysis of ways and means by which the extensive and elaborate indexing work done in the Research Documentation Section can be integrated not only into the central record system to improve its usefulness for program analysis, but also into other comprehensive indexing and scientific coding activities of NIH Institutes/Divisions and similar activities outside NIH, for example, in the National Library of Medicine and the Science Information Exchange.

There are also critical points of contact between the central data system and the budget office of NIH resulting in the development of tabulations to provide background data for the budget and financial management units. A further relationship, closely related to several of the preceding aspects, is also being worked out, i.e., the contribution which the central data system can make to the new DRG responsibility in the scientific evaluation of NIH programs.

The emphasis on the developmental aspects of the central data system has been influenced by interest shown in the Office of the Surgeon General towards making available more convenient and more consistent data for all PHS programs, and also by recent interest from the Office of the Secretary, HEW. These interests will further influence the type of system to be developed.

The broadened and reoriented work in this general field is directed toward utilizing the capacity of electronic computers to provide more versatile, more closely-knit, and more efficient services both in the administrative and the program planning processes of NIH.

Office of Associate Chief for Research Analysis and Evaluation

A new central resource in the Division will be coordinated by the recently-created Office of the Associate Chief for Research Analysis and Evaluation. This office will establish a program for the study and development of methods and systems to provide expanded facilities for the analysis, evaluation and scientific characterization of the research grant activities of NIH. Particular emphasis will be placed upon the evaluation of research areas and disciplines which have support from several institutes.

The new organization includes the existing Research Accomplishments Unit and a new Scientific Evaluation Section. The Accomplishments Unit will continue with its present assignments and functions. The Scientific Evaluation Section, with additional professional scientific staff, will enlarge the present capacity for DRG staff review of the current status of research fields. A predominant role, however, will be that of establishing a system for analysis and review of PHS-supported research fields by consultants and experts outside the Service. The services of experts will be secured in desired fields by research grant or research contract mechanisms. Close contact will be maintained with study sections and institutes for receiving recommendations both as to areas for study and consultants. Personnel of the new facility will act as project officers and as liaison staff for the provision of required data to the consultants.

In the performance of the scientific evaluation function, early studies will involve pilot models and prototype projects for improvement of current storage and retrieval systems which should lead to more centralized and complete information systems for rapid selective retrieval of scientific information relating to research grants. This activity will be planned and closely coordinated with efforts of the Associate Chief for Analysis and Statistics through the Statistics and Analysis Branch and the Research Documentation Section, DRG. Similarly, early studies planned will be the development of methology in the determination of evaluation parameters to be applied to research activities under study.

Two activities selected to enhance evaluation procedures are:

1. The establishment of a Scientific Evaluation Advisory Group made up of representatives from the Institutes and others in NIH who are working in program analysis and research evaluation in the Institute research programs. This group will act as a liaison between the scientific evaluation activities of DRG and those engaged in the Institutes and Office of the Director, NIH. Meetings would encourage exchange of methodological approaches to problems encountered in the analysis and evaluation of research grants activity.

2. The establishment of a registry of scientific review documents. This activity would receive, register and classify the scientific reviews and reports generated by institutes and divisions which evaluate the current status, growth and development of research programs in various scientific fields and areas relative to their

interests. On request, such a facility will report on analytical and evaluative reviews underway or finished in the components of NIH and act as an NIH-wide resource for information concerning research analysis and evaluation studies.

Specific activities completed since January 1, 1964, include:

1. A study of research support by PHS to Departments of Chemistry in U. S. colleges and universities, prepared by the Sub-committee on Chemistry, Committee on Science and Public Policy, National Academy of Sciences.

2. A comparison study of biomedical research programs of National Aeronautics and Space Agency and NIH.

Activities in progress are:

1. A study of PHS support for drug evaluation methods.

2. A study of research supported by PHS in the field of organ transplantation research.

Research Accomplishments Section

This Office's functions are as follows: (1) to promote accelerated communication between scientists in their respective fields; (2) to prepare analytical studies of ongoing research and research accomplishments in different scientific fields; (3) to identify and survey any "gap" areas where further research is seriously needed; (4) to make continuing longitudinal studies of "research potential"; and (5) to prepare background material for addresses at scientific meetings and for papers to be published in scientific journals.

The Office continues to promote the organization of information exchange groups, the first of which was started three years ago on an experimental basis in the field of Oxidative Phosphorylation and Terminal Electron Transport.

Two other information exchange groups in the areas of Blood Hemostatis and Computer Simulation of Biological Systems are now active and several others are in the planning state.

Biomedical scientists who have closely related research interests are invited to membership in an exchange group for the purpose of exchanging their research findings prior to the publication of their work in scientific journals. The vigorous interest of the many member-scientists, as well as others desiring to participate in these activities, suggests that the program will become an effective method for accelerating communication of research findings.

Examples of other activities are the promotional "100 Problems" program that has resulted so far in the publication of "100 Problems in Environmental Health" and "Some Problems in Oral Health"; the "forward-Oriented Reviews"

program leading to publication of reviews in limited areas showing what has been done and what needs to be done in the area; periodic polling of study section membership to identify recent research achievements of outstanding importance and to identify pressing problems that need attention.

Examples of studies of ongoing research have been a survey of NIH supported research in the state of Washington; NIH support of research on germ free animals; PHS support of research in schools of pharmacy; PHS support of research on pesticides; PHS support of research in entomology; PHS support of research in departments of pathology; and a worldwide survey including all sources of support of research on reproduction as related to birth and population control.

The Office of Research Accomplishments also undertakes studies which are basic to the preparation of papers for presentation at scientific meetings and publication in scientific journals. It also prepares background material for replies to congressional requests for information on the PHS programs and their management, including information on the Advisory Councils and PHS scientific personnel. Statistical data are prepared in support of the material mentioned.

Policy and Procedure Office

The Policy and Procedure Office has continued to be responsible for the formulation, implementation, and revision of policies and procedures for the NIH grant and award programs within the framework of PHS policies, and for initiating and conducting studies leading to the formulation of such policies on a PHS-wide basis.

Detailed substantive reviews of all extramural policies and procedures within the PHS are conducted to identify areas of omission or deficiency; new and modified policy for appropriate review and coordination is recommended; existing practices among the PHS granting institutions is coordinated; and problems and inconsistencies which proposed revisions in grant policies and/or procedures may create are anticipated.

The Office coordinates, promulgates, and disseminates grants policy to provide a central respository for PHS grant policy and procedure, and to assure a unified and coordinated approach to the development, review, and implementation of all PHS policies and procedures on grants and awards. The second edition of the Grants Manual, effective April 1, 1964, and the up-dating revisions reflect the changes that have been developed through PPO activities.

Patents Office

In January 1964, DRG assumed responsibility for processing invention reports from Community Health and Environmental Health grants and awards. Acceptance of this additional responsibility means that the Division is now servicing 23 institutes and divisions of PHS in this area.

A series of seminars on PHS patent policies and procedures governing inventions developed with PHS funds was held in October of 1963. A total of

206 persons attended 13 sessions. The seminars were designed to aid the administrative staff of the various institutes and divisions of the PHS in understanding PHS patent policy and procedures established to carry out its responsibilities in this area. A number of additional orientation conferences have been held upon request of the administrative staff.

Two brochures regarding patents were issued. One, entitled "Grant and Award Programs of the Public Health Service: Policies and Procedures Governing Inventions," was issued as an orientation document for use of staff in the various sponsoring institutes and divisions. The other entitled "Public Health Service Patent Policies and Procedures Governing Inventions" was prepared for use of the staff in grantee institutions responsible for administration of PHS grants and awards.

The institution of the Annual Invention Statement requirement in 1962 resulted in an increase of 69 percent in the number of cases reported to the service in 1963 over the number reported during 1962.

A major development in the patent area was the issuance of the President's Memorandum in October, providing an overall Government Patent Policy. This statement of policy recognizes that it is not feasible to have complete uniformity of practice throughout the Government in view of the differing missions and statutory responsibilities of the several departments and agencies engaged in research and development; nevertheless, there is need for greater consistency in agency practices in order to further the governmental and public interests in promoting the utilization of federally-financed inventions and to avoid difficulties caused by different approaches by the agencies when dealing with the same class of organizations in comparable patent situations.

The impact of the statement on DHEW patent regulations is under consideration.

Information Section

Information activities regarding the policies, programs, and achievements of the Division are planned and executed by the DRG Information Section. This Section also develops and releases information through a variety of media on the technical and administrative aspects of NIH and BSS extramural programs for support of research and training.

As the Division's responsibilities have increased with the expansion of PHS extramural programs, the Information Section has extended its services as the center for replies to a broad variety of public inquiries forwarded from NIH, BSS, and the Public Inquiries Branch of the Office of the Surgeon General, as well as other governmental and non-governmental agencies.

The Information Section writes releases for publication; prepares speeches and other materials; provides the working press with assistance as needed; prepares weekly reports on program developments for the Surgeon General; and handles inquiries from the public.

The DRG Newsletter was initiated in 1964. The Newsletter conveys program information, particularly in the grants management area, to provide grantee officials with interpretation of grant management procedures.

During 1963 and early 1964, the Information Section increased its audiovisual program to facilitate more effective technical and scientific communication. Four exhibits now in use were staffed by information specialists of the Section and other Division personnel at numerous scientific meetings throughout the country.

The DRG Reference Room was reorganized in 1964 to make material more readily available to the DRG staff. The Reference Room serves as a repository for scientific journals and other published materials. To provide information on grant and award activities, the Reference Room maintains a current Grantee Institution File on research developments, personnel changes, press releases, etc., in insitutions that receive PHS extramural support.

Grants Associates Program

Ten candidates who formed the initial 1962-1963 class of the Grants Associates Program have completed their training and accepted permanent assignments within NIH. Eleven candidates make up the second group to embark upon the 12-month training period designed to develop qualified professional staff for the various grants programs throughout PHS. Six reported for duty late in 1963 and five began their training early in 1964.

Each graduate was offered several positions in the extramural program. Positions accepted are those of assistant to the Associate Director for Research Grants, Office of the Director, NIH; staff scientist, NICHD; assistant chief, Research Grants Branch, NIDR; executive secretary, Health Services Research Study Section, DRG; assistant head, Foreign Grants and Awards, Office of International Research, NIH; staff scientst, Research Grants Branch, NCI; head, Mental Retardation Centers Programs, NICHD; assistant chief, Grants Management Branch, DRG; training consultant, NICHD; and scientist administrator, Scientific Evaluation Section, DRG.

Planning for the Grants Associates Program began in 1961 under DRG leadership as a step toward alleviating the increasing problem of recruiting and efficiently utilizing competent scientist administrators. A Board of Directors consisting of senior scientist administrators was appointed by the Deputy Director of NIH to develop objectives and policies and to solve the practical problems relating to organization and administration.

The 12-month on-the-job training program involves experience in grants administration, including preliminary scientific review of grant applications, manpower support (training grants, fellowships, etc.) and overall grants management.

Grants associates are carefully selected from scientists possessing a doctoral degree in a health-related science such as medicine, the biological and behavioral sciences, public health, and selected physical sciences. In

addition to having a basic interest in the development and management of federally supported research, those selected to participate in the program must have demonstrated their ability to do research as well as a potential for science administration.

A cornerstone for the program's success is the preceptor selected for each of the associates. Each preceptor is a senior scientist-administrator who has had extensive experience in grants administration in the Public Health Service and also serves as a member of the Grants Associates Board. He carries the primary responsibility for designing his associate's training. In practice, this is done in close consultation with the associate, the Executive Secretary of the Program, and various other members of the Grants Associates Board.

During the year, three seminars are conducted for the Associates. One entitled "Public Administration" is presented to all associates and a small number of extramural scientific staff in the Research Grants area. This is conducted by the School of Government and Public Administration of American University and features recognized authorities in the field of government and public administration. The second presents an overall view of PHS programs with discussion centering on the establishment of policies and program. The third is informal in nature, designed to encourage laboratory scientists, scientist administrators from NIH and other agencies, university deans, and directors of training programs to share their knowledge and thoughts on programs relating to federal support of research and training.

Logistical support of the program is provided by the Office of the Chief, Division of Research Grants. The Executive Secretary is a member of the Employee Development Section, Personnel Management Branch of the Office of Administrative Management, NIH.

The administrative staff of the Research Grants Review Branch has been significantly expanded since calendar year 1962 in order to meet the increased complexities involved in processing and reviewing applications for all of the PHS research grant programs administered by NIH and the Bureau of State Services.

New offices are those of a Deputy Chief, an Assistant Chief for Review, and an Administrative Officer.

Study sections have increased in number from 46 to 51, reflecting the needs that evolved during 1963 to create new sections for certain disciplinary areas and to divide the workloads of others. The new groups are Applied Physiology, formerly an advisory committee, and the Disease Control Study Sections, the latter with a broad area of review for research in the detection, prevention, treatment and control of disability, and specific chronic and communicable diseases in the community. Those that have recently been divided into A and B parallel groups are the Surgery and Allergy and Immunology Study Sections. The Program Project Committee on Arthritis and Metabolic Diseases of NIAMD has been transferred to the Branch and a Child Health Program Project Committee is being established.

During the four Advisory Council periods from January 1963 through June 1964, study sections processed and reviewed 13,230 research proposals: 3,147 during the March 1963 period, and 10,083 in the ensuing periods through March 1964. Although not an equal period for comparison, the total was 10,028 for calendar year 1962.

Considerable research has been done by the DRG staff, as requested by the Research Development Committee, in the programming of activities of the study sections to stimulate research over the 16-year period from 1946 to 1962. A paper summarizing some of these programmatic activities has been accepted for publication by Science magazine.

The Study Sections

In addition to conducting the technical review and appraisal of research applications for recommendations to the Advisory Councils, the 51 study sections of DRG continued to stimulate research in neglected areas of health, medical and related sciences.

They also reviewed the status of research in specific health areas to determine what action should be taken to improve future research.

As a result of the marked interest in the screening of chemicals and plant extracts as potential drugs, several study sections joined forces in

planning a conference on "Evaluation and Mechanism of Drug Toxicity."

The study sections also intensified their efforts to interest top level students from basic science disciplines in graduate study in the environmental sciences. Universities have been urged to expand their curricula to include pertinent courses and collegiate schools of nursing have been urged to develop a research climate.

Through sponsorship of study sections, meetings and workshops were held to bring study section members and other scientists throughout the country up to date on developments in particular fields of interest. These meetings have resulted in numerous publications effecting far wider dissemination of information than would have been otherwise possible.

Some of the significant activities within the study sections during the 18-month period of this report follow:

Accident Prevention Research

Forty-six applications for research grants were reviewed by the Accident Prevention Research Study Section in 1963. Two-thirds of these were directed at some phase of the motor-vehicle accident problem.

As in previous years, this type of accident has commanded more than its share of research attention in comparison with the relative numbers of disabling injuries and deaths from home, public, recreational and occupational accidents.

Grants in 1963 amounted to $1,647,381, a small portion of which financed projects reviewed by other Study Sections. In addition, a research contract for $180,000 was awarded for construction of a partial simulator to be used in testing driver behavior under conditions resembling turnpike traffic. This proposal was reviewed favorably by this Study Section.

Only one-fourth of the Study Section members are actively engaged in accident prevention research, the others being occupied in the disciplines that are components of this multi-disciplinary field. It is to be expected that the opportunities of the latter members to foster and stimulate research by other scientists in the field are limited and have not been bountifully productive of high-grade research proposals.

Despite the decreasing number of grant applications coming to the Study Section for review, it has continued to apply high standards in assessing proposals. Thirty-seven percent of the applications were recommended for approval, about the same proportion approved in other years.

During 1963 the Study Section benefited from evaluative reviews of four completed projects and one partial study prepared by the research psychologist of the Division of Accident Prevention's Research Grants Section. These have permitted comparison of expectations of the proposals before funding with the results achieved by the investigators.

Though the achievements fell somewhat short of the initial promises, the apparent reasons for the shortcomings provide helpful guidelines to the review group in considering future applications.

Bacteriology and Mycology

The Bacteriology and Mycology Study Section reviewed a total of 361 applications and made 28 project site visits during 1963, compared with 345 applications and 20 project site visits in 1962.

Four Study Section members retired at the end of the spring meeting after four years of distinguished service. Five new members were appointed and two members were transferred from the Environmental Sciences and Engineering Study Section, making a total of 21 members.

A joint meeting of a special committee from the two Surgery Study Sections and the Bacteriology and Mycology Study Section was held March 8, 1963 at NIH to explore the possibility of stimulating clinically-oriented research in bacteriology and improving the quality of proposals received from applicants. This meeting brought forth a number of helpful suggestions for further consideration.

Behavioral Sciences

The Behavioral Sciences Study Section reviewed 215 applications in the general areas of social psychology, psycholinguistics, social psychiatry, sociology and anthropology at three meetings during 1963, of which 40 percent were recommended for approval.

Advisory Councils who gave final review concurred in all but two of the recommendations.

Professor Ralph Turner of the University of California, Los Angeles, was appointed as a new Chairman and three new members were added to the Study Section: Dr. Benson Snyder of the Massachusetts Institute of Technology, Dr. Quinn McNemar of Stanford University, and Dr. Gresham Sykes of the American Sociological Association.

Biochemistry

The Biochemistry Study Section reviewed a total of 305 applications during 1963. Of these, 221 or 72.4 percent were approved, 79 or 25.9 percent were disapproved, and five were deferred.

The total projected dollar expenditure requested was $26,074,730. Of this, $14,252,391, or an average of $20,712 per grant per year, was recommended for approval.

Priority scores ranged from 100 to 407 with medians of 200, 209, and 211.

Dr. Paul D. Boyer of the University of California, Los Angeles, replaced Dr. John M. Buchanan of the Massachusetts Institute of Technology as Chairman

of the Study Section in September.

Cardiovascular

The Cardiovascular Study Section's review of 330 applications during 1963 was a decrease of 14 percent compared with 385 reviewed in 1962.

Of the total, 192 were recommended for approval and 129 for disapproval.

Section members made eight project site visits concerning separate applications.

Pressure of a heavy workload made it impossible for the Section to hold discussions concerning the adequacy of research being conducted in the specific areas with which it is concerned. Realizing this is a pertinent function of advisory consultants, Section members have since incorporated time for appropriate discussion sessions. The year's heavy workload also precluded bringing ad hoc consultants together to discuss developments and needs in a specific area as has been done in previous years.

Cell Biology

Approximately 350 applications reviewed by the Cell Biology Study Section during the year ranged in subject matter from cellular biochemistry, including nucleic acid metabolism, to electron microscopy; from normal embryology to the neoplastic growth of plants and animals; and from the anatomy of vertebrates to the ecology and development of land and marine invertebrates and single-celled organisms.

Largely instrumental in founding the American Society for Cell Biology, the Study Section again participated in the annual meeting of the society which now has 1,029 members. The third annual meeting, held in New York City in November, 1963, was attended by nearly 2,000 scientists. Recent and current Study Section members who guided the meeting included Dr. Hewson Swift, president-elect and panel chairman; Dr. Rollin Hotchkiss of the annual meeting's local committee; and Drs. Heinz Herrman and Joseph Gall, panel chairmen.

Several signal honors were received during the year by other recent and current members of the Study Section.

Dr. F. C. Steward was awarded a Guggenheim Fellowship to enable him to concentrate on his studies of plant morphogenesis; Dr. Morgan Harris was appointed a member of the National Advisory Council of NIGMS; Dr. Hewson Swift became the fourth president of the American Society for Cell Biology; and Dr. Mac Edds, Chairman of this Study Section, became Chief of the Division of Medical Sciences at Brown University to organize the new medical school there.

Chemotherapy

The Chemotherapy Study Section was reorganized, renamed, and to some extent, redirected during the year.

This Study Section was previously called the Cancer Chemotherapy Study Section, and as such, reviewed primarily those applications proposing investigations of biological activity, toxicity, cytological or biochemical mode of action and large scale clinical trials of candidate cancer chemotherapeutic agents. However, the competence of Study Section members made it feasible for this group to review applications aimed at the chemotherapy of other diseases as well as cancer.

The changed name of the Study Section properly reflects these broader responsibilities. The Chemotherapy Study Section is interested in stimulating interest in and improving the quality of applications for research in the use of tissue culture techniques in the selection of specific chemotherapeutic agents for individual treatment of cancer patients. A committee of the Study Section has developed tentative plans for an informal 1964 meeting of an educational nature which might include a number of investigators already interested in the field.

Upon the retirement of five members in June of 1963, six new members joined to bring the Study Section's membership to 14.

At its September meeting, the Study Section reviewed seven applications for career or career development awards. In several cases, applications for research career development awards and for research grants which concerned the same investigator were considered together. The Study Section welcomed this additional responsibility and regarded it as an appropriate one that could be handled effectively by scientists with special competence in the areas of investigation of the applicants.

During the year, the Study Section reviewed 158 applications, recommended 80 for approval, 71 for disapproval and 7 for deferral pending project site visits. Twenty-six project site visits were made, including the 7 mentioned. Applications for research in chemotherapy of diseases other than cancer, increased during the year from 1 of 55 in January to 5 of 58 in September. This shift of emphasis may be expected to be more pronounced in the coming year.

Communicative Sciences

The Communicative Sciences Study Section reviewed 147 applications during 1963 of which 78 were recommended for approval, 64 for disapproval, and 5 deferred for project site visits.

The April meeting of the Study Section was held at Hollywood, Florida, in connection with the annual Triologic Society meeting. This afforded an opportunity to explain NIH's interest in research in otolaryngology.

The Study Section has lately been concerning itself with methods of improving the quality of research grant applications in the area of speech and hearing. A subcommittee was formed to study this problem, and gave its first report at the September meeting of the Study Section. Several ideas were presented, one of which was the possibility of an informal meeting with the Communicative Disorder Research Training Committee of NINDB to discuss

methods of improving research training in the field, and thus, ultimately, the quality of research grant applications.

Other programming activities considered by the Study Section for possible future implementation are: A conference on research areas needing further exploration; a conference on auditory electroneural physiology; and a symposium on the composition, function and fate of endolymph and perilymph in the labyrinth of the ear.

Computer Research

The Computer Research Study Section replaced the Advisory Committee on Computers in Research in January, 1964. A final report, reviewing the past three-year activity of the Advisory Committee, is being prepared for presentation to the Director, NIH.

Feeling that the development of laboratory computers is an important contribution to biomedical data processing, the ACCR endorsed a LINC Evaluation Program which is currently being supported by NIH. An announcement in Science (issue of 2/22/63) invited biomedical scientists to participate in evaluating the usefulness of the Laboratory Instrument Computer (LINC), a small stored-program digital computer developed at Massachusetts Institute of Technology's Lincoln Laboratory. Selected participants would assist in assembling a LINC and provide an evaluation after using it in their own research.

Approximately 72 written proposals for consideration were submitted by investigators throughout the country. A special review group, including representatives of ACCR, conducted a critical scientific evaluation of these requests and chose 12 investigators whose participation would be likely to make the most effective contributions for the purposes of the program.

Each of the 12 investigators was awarded a LINC computer for installation in his laboratory to be utilized in his specific research projects and the value of its performance reported. After 18 months of trial and exchange of information, the Evaluation Board plans to prepare a final report and set of recommendations concerning the performance of this machine in a laboratory environment. Six of these awards were approved by the National Advisory Mental Council for funding by NIMH, and six were approved by the National Advisory Health Council for funding by DRFR.

Sixty project site visits were conducted during 1963 in the review of 102 applications assigned to ACCR. Five additional site visits were made in the review of 12 applications assigned for ad hoc review. There were 69 recommendations for approval.

Dental

The Dental Study Section continues to sponsor and organize conferences designed to encourage research in the many areas of science related to dental health.

Plans were initiated in 1963 for organizing a conference on dental pulp to which basic scientists in various fields of research will be invited. A planning committee, with Dr. Sidney B. Finn as chairman, held two meetings and developed a tentative program. The Study Section approved a motion for support of the proposed conference with Dr. Finn as principal investigator. The target date is October, 1964, with Palm Springs, California, as the probable site.

A meeting of the planning committee for a repeat Conference on the Salivary Glands was also held. This conference will be held about two years hence. Dental Study Section members suggested that it might be desirable to sponsor future conferences covering the fields of oral physiology, electromyography and occlusion.

Dr. Robert E. Moyers reported on the Study Section-sponsored Dental Research Conference in Sensory Craniofacial Innervation, held in Rochester, Minn., September 9-10, 1963. A number of superb papers were presented and there was a good exchange of ideas. The cordiality and hospitality of the Mayo Foundation contributed to the favorable environment. The Study Section representatives believe this was a highly successful conference which should be repeated in three to five years.

Study Section members have agreed to work with NIDR in an effort to arrange Sigma Xi lectureships to stimulate interest in dental research.

During 1963, the Dental Study Section reviewed 233 applications of which 130 were recommended for approval, 76 for disapproval, and 27 for deferral.

Endocrinology

Programs involving the preparation and distribution of pituitary hormones and radioactively labeled steroids increased during 1963. Through the efforts of the Endocrinology Study Section, a National Pituitary Agency was established. The Agency acts as a collecting center and clearing house for human pituitary glands and hormones to be utilized in hormone research. It is anticipated that the activity of the Agency will facilitate the recovery of human glands and perhaps develop similarly to the existing eye-bank collection.

A contract between the Medical Research Council of the United Kingdom and NIH has been initiated under which commercially unavailable and rare steroids will be made available in limited amounts to qualified investigators.

Human growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, and bovine growth hormone have been prepared in highly active form and distributed to research establishments throughout the world. The number of requests for pituitary hormones continues at a rate of 300 to 400 annually.

Urinary Gonadotropin of high potency for use as a standard, prepared by Dr. Alexander Albert of the Mayo Foundation under an NIH grant, has been added to the program and is being distributed world-wide.

Since the first of the year a notice has appeared monthly in Endocrinology listing materials currently available under the auspices of the Endocrinology Study Section. During the year, 4-C^{14} aldosterone has been added to the list of radioactively labeled steroids. A description of materials and the procedure for obtaining them is available in a recent notice issued by the Section.

A workshop on estrogens was held in Eastsound, Wash., May 22-25, 1963. The proceedings were to be published in book form to be available in March, 1964.

Proceedings of the International Conference on Neuroendocrinology held in Miami, Fla., December 6-8, 1961, under an NIH grant, have been published. The book, "Advances in Neuroendocrinology," edited by A. V. Nalbandov, has been widely distributed.

A Subcommittee on Standards has been appointed by the Committee on Hormone Distribution to encourage the establishment of uniform assays and standards. It is anticipated that representation will be had on future discussions in which world-wide standards are considered.

Approximately 450 applications for grants in aid of research are reviewed annually by the Endocrinology Study Section, with resultant recommendations being made to respective Councils.

Environmental Sciences and Engineering

During 1963, this Study Section continued to review applications in the four major areas of air pollution, water pollution, food sciences (microbiological aspects), and occupational health. Rather than split the Section to relieve an increasing workload, applications in the areas of food sciences and occupational health are now assigned to the Study Sections of Bacteriology and Mycology, and Toxicology and Physiology because of their equal competencies for review and interests in these fields. Since January 1964, this Study Section has been concerned primarily with applications for water and air pollution control research.

During the year a total of 270 applications were evaluated with 55 percent recommended for approval, in the amount of $2,714,000.

In the air pollution field, applications were reviewed on fundamental studies of the atmosphere as it relates to estimation, determination or evaluation of gases, liquids or particulate components and of the chemical and physical reactions which occur among them.

In the food sciences, proposals were reviewed on milk and food including effects of chemicals, microorganisms, temperature, humidity, radiation, packaging, shipping and storing, as related to keeping and nutritive quality, palatability, and safety.

In the occupational health area, applications were considered on

development of diagnostic and preventive measures related to disease, pathologic changes or physiologic alterations arising out of the work environment.

In the water area, applications were submitted primarily on detection, determination, and evaluation of all types of hazards involved in use and reuse of water, and waste water relating to the conservation of water for public water supplies; chemical, physical, and biological techniques for examination of water and waste water, including their application to the development of criteria and standards; fundamental principles such as surface chemistry, colloids, absorption phenomena, and gas transfer as applied to water and waste water.

The Program Planning Committee of the Section, organized in early 1962, has continued to make progress in conformity with its expressed objectives to:

> Determine means of securing top level students from basic science disciplines for graduate study and specialization.
>
> Arouse interest in university faculties to the expanding programs and needs in the environmental sciences.
>
> Attract highly trained basic scientists to research and teaching careers.
>
> Cooperate with other professional groups with similar objectives and interests, for example: the research committees of the American Sanitary Engineering Intersociety Board, Water Pollution Control Federation, American Water Works Association; other Study Sections with related interests such as Toxicology, Parasitology, and Tropical Medicine Sections; the National Research Council Committee on Environmental Health; the National Science Foundation; international groups such as the Pan American Health Organization; and the Bureau of State Services.
>
> Develop and plan conferences and symposia for the purpose of stimulating new concepts in research and training and dissemination of information.
>
> Study undergraduate and graduate school curricula for training personnel and definition of the areas and disciplines that should be included and emphasized.

During 1963, the Planning Committee, consisting of seven members under the chairmanship of Dr. Hovhannes Heukelekian, met three times. Following are activities undertaken by the Section as a result of Committee recommendations:

(1) The Study Section planned to sponsor a Conference on Graduate Opportunities in Environmental Health to be held at the Harvard School of Public Health with Dr. James Whittenberger as the Principal Investigator. The intent of the Conference would be to exchange information in the New

England area on research needs and career opportunities and sources of scientific manpower to satisfy these needs.

(2) An application, co-sponsored by the Toxicology Study Section, has been evaluated for a Conference on Use of Chemicals in Agriculture to be held at Davis, Calif. The Conference will examine critically the techniques in assessing any direct or indirect hazards of chemicals and food additives and review and integrate the present status of knowledge in the controversies arising from the use of pesticides, herbicides, and insecticides.

(3) The Planning Committee pointed out that one of the major areas of environmental sanitation which has suffered from a lack of research is that of solid waste disposal.

In order to stimulate research in this field, the Study Section proposed a National Conference for Research on Solid Waste December 2-4, 1963, in cooperation with the American Public Works Association and the Division of Environmental Engineering and Food Protection, PHS, at the University of Chicago Center for Continuing Education. It is anticipated that the findings of the workshop sessions will set a pattern for future research.

(4) Upon approval by the Study Section to explore the possibilities of cooperating with other agencies that have interests in biological oceanography, a subcommittee met in Bethesda July 15, 1963, with the Planning Committee. Invited to participate in the discussion were Dr. Irvin Fuhr, Executive Secretary of the Biophysics and Biophysical Chemistry Study Section, and Dr. J. E. King of the Bureau of Fisheries, Department of the Interior. The Subcommittee was instrumental in arranging talks presented at the September 9-11, 1963 Section meeting by Mr. Robert Abel, Executive Secretary, Interagency Committee on Oceanography, who spoke on "Impact of the Oceans on the National Welfare" and by Dr. Ross F. Nigrelli, Director of the Laboratory of Marine Biochemistry and Ecology, New York Aquarium, who spoke on "Biological and Chemical Approaches in Oceanographic Studies."

As a result, the Study Section is cognizant of the overwhelming field that could be included in the marine sciences and that it must still make decisions relative to its own responsibility in this area of research.

For further orientation of Study Section members on problems relating to oceanography and information that would be derived in developing and fostering needed research in this area, the Section arranged to meet at the Institute of Marine Sciences of the University of Miami in connection with its regular meeting in January, 1964. Lectures were given by members of the staff, pertaining to research in aquatic biology and oceanography, and members of the Section observed research projects currently in progress.

(5) Upon approval of the Study Section at the April-May 1963 meeting, a Subcommittee was appointed to explore the needs for a book on the concepts of chemistry as applied to water analyses.

The Subcommittee presented its ideas and findings at the January, 1964

meeting, emphasizing its conclusions that the book should provide guidance in the use and interpretation of analyses for constituents in water. They further stressed the necessity for a thorough understanding of analytical chemistry and the fundamentals of chemistry in solving an analytical problem.

All recommendations of the Program Planning Committee are presented to the full membership of the Section for final consideration and Grants Branch Chiefs of all Environmental Health Divisions, BSS, are invited to participate in discussions at Planning Committee meetings.

Experimental Psychology

The Experimental Psychology Study Section reviewed a total of 250 applications during 1963, of which 63 percent were given a favorable recommendation.

The Section completed plans to sponsor a workshop on ethology and experimental behavioral analysis in Rome, Italy, June 15-20, 1964, supported by an NIMH grant. Invitations were extended to 17 European ethologists representing a broad spectrum of ethological approaches from countries including Great Britain, Norway, Italy, the Netherlands and West Germany. Six members of the Study Section and the Executive Secretary were to participate.

General Medicine

The General Medicine Study Section reviewed 310 research grant proposals during the calendar year 1963. Of these, 34 dealt with various phases of rheumatic and arthritic disease, 85 were gastroenterological proposals, 35 were internal medical studies dealing mostly with endocrinological and other metabolic disorders, and 56 were dermatological projects. Applications for study of renal disease totalled 39, while 33 were concerned with liver disease. Of the total number of proposals, 51 percent were recommended for approval, 41 percent for disapproval, while 8 percent were deferred for further study after initial review. Total funds requested were $7,041,953; total funds recommended were $3,018,742.

A symposium on dermatologic research, "The Biology of Keratinization," was convened at the UCLA Lake Arrowhead Conference Center. Manuscripts presented at the symposium were published by Academic Press and distributed early in 1964. The conference accomplished much in elaboration of research interests in dermatology.

A workshop on clinical research was held in Alaska in August of 1963. Responsible officials in Alaska responded favorably to the visit by Study Section members and Institute representatives. The group visited various clinical centers to observe facilities and clinical subjects available for studies. The Alaska Science Conference was attended by Study Section and staff members from NIH. A detailed report was completed in December.

Genetics

A continuing aim of the Genetics Study Section is to encourage the sound expansion of genetic research and to provide realistic assistance to this field.

During 1963, a major effort was brought to successful conclusion in the publication of the second and third of a series of three volumes on genetic methodology entitled "Methodology in Mammalian Genetics" and "Methodology in Basic Genetics," edited by Walter J. Burdette, and published by Holden-Day, Inc. of San Francisco.

Information for these publications was developed through a series of symposia planned and carried out by the Genetics Study Section in 1961 with financial support from the Division of General Medical Sciences, now NIGMS.

The three volumes provide a compendium of practical resource information to aid research workers in broadening the scope of their genetic investigations.

During 1963, the Genetics Study Section reviewed 233 research grant applications of which 147 were new proposals, 61 sought continued support and 25 were for supplements to current grants. Altogether, 174 applications were recommended for approval, 43 for disapproval, and 16 were deferred for project site visits or additional information.

Hematology

Carefully watching developments in the field of hematology, this Study Section has given priority to supporting projects in which the research is basic as opposed to clinical. Its aim has been to channel grant funds towards research intended for elucidating unsolved problems and basic mechanisms. While the value of clinical research is recognized by the Study Section, the collection of data in the hematology or clinical pathology laboratory is considered as deserving of grant support to a lesser degree than projects designed to study problems in depth.

Hence, the Study Section has continued to play a role in fostering development in newly-emerging lines of hematology research.

Following a series of conferences held in previous years in the broad field of coagulation, a conference was sponsored by the Study Section on erythropoiesis, i.e., the mechanism of red blood cell formation, proceedings of which were published later in a book entitled "Erythropoiesis," (Grune & Stratton N. Y.) edited by Dr. Leon O. Jacobson. The conference, supported by an NHI grant and sponsored jointly by the Study Section and the University of Chicago, was held in San Francisco in January of 1962, with 83 participants and discussants from the U. S. and eight foreign countries.

Since 1960 a subcommittee of the Study Section has been instrumental in distributing erythropoietin, a hormone-like substance produced under an NHI grant, to interested research workers. The supply of this material produced from the blood plasma of anemic sheep is largely exhausted.

The Study Section felt that by handling the material and reviewing the progress made in the investigations on erythropoietin, and finally arranging the conference, the stimulating pioneer steps have been completed. Therefore, this function for making erythropoietin available in the future and programming the erythropoietin research was transferred to NHI. For this purpose, formation of a standing committee by the extramural program of NHI was largely completed in the last months of 1963.

In co-sponsorship with the National Hemophilia Foundation, the Study Section recommended approval of a PHS grant on a cost sharing basis to cover part of the expenses of a conference on hemophilia and the publication resulting from it. The conference, December 7-8, 1963, in Washington, D. C. was organized by Dr. Kenneth M. Brinkhous, a past Chairman of the Study Section.

Future plans for smaller round-table type of conferences have been considered.

The Study Section reviewed 283 applications in 1963, compared with 291 in 1962. In both years, about 60 percent of the applications were approved, and an additional 5 to 8 percent were approved after site visits. Thus, approximately two-thirds of the applications were recommended for approval.

History of the Life Sciences

As in the past, this Study Section continues to provide preliminary review both of research grant applications and fellowship applications. The number of applications reviewed during 1963 increased slightly in both categories, over 1962. The Study Section recommended 53 percent of the research grant applications and 64 percent of the fellowship applications for approval. All recommendations were sustained by the National Advisory Councils.

Most of the applications reviewed continue to be in research areas supported by NIGMS - about 50 percent; and NIMH - about 33-1/3 percent; but review was also made of applications from three other institutes or divisions.

In the last four years, the Study Section has reviewed applications from all but two of the nine Institutes and also from two Divisions of the Bureau of State Services. This is a strong demonstration of the wide applicability of the historical method for illuminating research areas.

Three principal goals in general programs have been identified and pursued: 1) A programming goal which is part of the continuing mission of the Study Section as a whole; and 2) and 3) administrative goals inherent in the responsibilities of the Executive Secretary.

(1) To survey and assist the development of research in the field of the history of medicine and health-related sciences. To further this goal, the Study Section had broad preliminary discussions at its January meeting. To explore further the problems of the field, a special Study Section meeting was held at Bethesda in March, 1963. At this meeting, members identified in detail many of the needs of the field. Since many of these needs touched upon

the basic problem of facilities for teaching and training, the Study Section voted to create a committee to explore means of conducting a thorough survey of the teaching of the history of medicine and health-related sciences in the United States.

In its subsequent preliminary work, this committee established a cooperative relationship with the History of Science Society in order to benefit from a questionnaire on teaching in the field which was being distributed by the Society.

Another committee was formed in September to determine with greater precision than before the needs for and feasibility of additional institutional facilities in the United States for graduate training in the history of medicine and the life sciences.

(2) To interpret to scholars in the field the special interests and views of NIH regarding historical research as a useful tool for scientific research. In furtherance of this goal, the Executive Secretary has provided information to the leading professional societies, university departments, and scientific journals in the field and has established continuing relationships with their leaders or editors. In 1963, furthermore, he gave informal talks about NIH support of relevant historical research to the general membership of three professional societies.

(3) To advance, within NIH and the PHS, the usefulness of historical research and the availability of its results to scientists. One important step in furtherance of this objective is the Study Section's sponsorship, together with the National Library of Medicine, of the May 1964 meetings of the American Association for the History of Medicine. The Executive Secretary, as Chairman of the Local Arrangements Committee and Member of the Program Committee, participated in planning the meetings.

The administrative staff continues to assist Dr. George Rosen in matters connected with his research project on "A History of Health Research in the United States." This project should be of particular interest and value within PHS because of its focus upon NIH during the past 25 years. The Executive Secretary has also initiated a number of independent historical studies which related in varying degrees to aspects of Dr. Rosen's project.

At the request of the Research Development Committee of RGRB, the Executive Secretary has done considerable research in the programming or stimulative activities of DRG Study Sections over the 16-year period from 1946 to 1962. With the Committee members, he is preparing an article based upon this research. This exercise in contemporary history strongly illuminates the desirability of having comparably detailed historical studies of the stimulative activities and internal research of all NIH Institutes.

Human Ecology

During 1963, the Human Ecology Study Section reviewed a total of 149 applications, of which 49, or 32 percent were recommended for approval.

Three members retired from the Study Section in June and five new members joined at that time, including an assignee from the U. S. Army. The Study Section now has a total of 14 members.

This increase in membership is appreciated since it is recognized that the number of applications reviewed per meeting, though not large numerically, present a heavy work-load, owing to the complex, multidisciplinary nature of each application.

An analysis was recently made of the 309 applications reviewed by the Study Section since its inception in September 1960, up to and through the meeting of January 1963. Results of the analysis disclosed:

(1) The overall average approval rate was 44 percent.

(2) The average priority score for approved applications was 227.

(3) Applications were reviewed from all Institutes of NIH and various Divisions of BSS.

(4) Over 20 percent of the applications received were from foreign countries or were classified as domestic/foreign.

(5) Approximately 20 percent of all applications were of such magnitude or complexity that a project site visit was made to obtain sufficient information for an adequate review.

(6) Nearly 40 percent of all applications involved a total budget of $100,000 or more; some 20 percent of these applications were approved only after the amount or time requested had been reduced by Study Section recommendation.

(7) The type of application reviewed usually contained demographic and epidemiological components, and the projects typically required a team of researchers, including an epidemiologist, a biostatistician, and a social scientist.

(8) Heart disease and cancer were the two disease entities of most frequent interest to the applicants whose proposals were reviewed.

(9) The chief reasons for disapproval of applications included: weak design, unrealistic aims of the study, and lack of clearly stated hypotheses.

The Study Section has continued to consider ways and means for improving the quality of community-based research throughout the world, with recognition of the importance of carefully planned, cross-cultural studies.

Human Embryology and Development

In addition to the review of applications, this Study Section has engaged in activities designed to raise the standards of research in the field of human embryology and development, and to focus attention on recruitment problems of vital importance:

Programming in Developmental Biology. At the 1963 April meeting of the Study Section, the need to expand research potential in the entire field of human development was reaffirmed. The Study Section strongly urged that the work of its existing Subcommittee concerned with programming in developmental biology should continue with plans previously outlined.

To help meet the acute problem of recruitment into research careers in this field, the National Advisory Council of NICHD approved a grant to support an Institute in Developmental Biology which was held at the University of Wisconsin, Madison, June 22-26, 1964, with Dr. Ben H. Peckham as Chairman of the conference.

Drug Testing for Effect on Embryonic Development. The Study Section continued its role with the Inter-Study Section Committee which is concerned with drug testing and drug effects on embryonic development. Numerous meetings of the Committee during 1963 resulted in planning and support through NIGMS of a conference on drug action, "Evaluation and Mechanism of Drug Toxicity," held in New York City in March 1964, under auspices of the New York Academy of Sciences. In addition to this Study Section, the Committee includes members of the Study Sections of Pharmacology and Experimental Therapeutics and Toxicology.

The Executive Secretary presented a paper entitled "Current Research Activities in Congenital Anomalies in the United States," at the third annual meeting of the Congenital Anomalies Research Association of Japan, July 5, 1963, in Nagoya. Visits were made also to Tokyo Medical and Dental University, Kyoto University, University of Osaka, Osaka City University, and the Atomic Bomb Casualty Commission Laboratory in Hiroshima.

During 1963, this Study Section reviewed a total of 308 applications requesting a total amount of $24,397,999. Of these, 167 applications in the amount of $8,008,227 were recommended for approval, representing 54.2 percent of the applications reviewed and 32.8 percent of the amount requested.

Medicinal Chemistry A and B

The January 1963, Study Section meetings were the first to be held after a division of the original section. The new A and B sections are parallel in some subdisciplines but each has its special competencies.

A total of 380 applications were reviewed during the calendar year, 62 percent of which were recommended for approval. This is about eight percent greater than for the previous year. The Institute assignments were as follows: GM 42 percent; CA 25 percent; AM 11 percent; AI 8 percent. The remaining 14 percent were divided among AP, EF, HE, MH, NB, RH, and DE.

The two sections are ever mindful of their responsibility to evaluate the scientific merit of proposed research and to advise the Institutes on the relation and value of the studies to the health sciences.

In an effort to promote studies of structure-activity relationships through cooperation between research chemists and pharmacologists, the booklet, "Biological Testing Facilities" was compiled and published by the Medicinal Chemistry Study Sections. Thirty-four laboratories are listed together with the drug actions under study in each.

Mental Health A and B

Divided into two parallel review groups in 1962, Mental Health Study Sections reviewed a total of 316 research grant applications during 1963, of which 112 were approved and 204 disapproved. Dr. David Pearl replaced Dr. Mordecai H. Gordon as Executive Secretary of Section A, and Dr. Frank Freeman continued as Executive Secretary of Section B.

Both Study Sections are concerned with means of stimulating development of research where needed in several areas of mental health. For instance, noting the paucity of research proposals dealing with schizophrenia despite the importance of this disorder, Section A is considering promotion of a conference covering this field.

Other suggestions discussed by the Study Sections in line with their programming responsibilities included regional or local consultative services to investigators sponsored by NIH; seminars, summer fellowship programs, discussion of the research grants program at professional meetings, and development of a nomenclature of mental health terms.

At the September meeting, Section A recommended to the NIMH National Advisory Council that it consider an announced program of planning grants to publicize the willingness of NIMH to support reviews of the literature and other activities involved in planning. It was felt this might serve to restore several potentially promising projects that are unacceptable at present because of inadequate planning or that need to be made more visible through explicit labelling.

B Section is planning to sponsor a Symposium on the research aspects of the Community Mental Health Centers Program, and a working committee has been appointed to develop plans and prepare for further discussion and action. A need has been seen for careful planning in support of the program to determine what research data are available and what the goals of research should be in evaluating: (1) the needs, attitudes, and contributions of the community to the program; (2) the best methods of operation of the Centers; and (3) the means of determining the effectiveness or results of such a program.

It is anticipated the symposium would result in development of procedures by which the Section could advise the NIH staff about research needs arising in connection with the program and would provide guidelines for evaluating research grant applications which bear upon the problems of the Community Mental Health Centers Program.

The usefulness of conferences for stimulation of research were evaluated, and a mail survey involving open-end questions was conducted among participants in a research conference held a few years ago. The consensus of respondents was that such conferences were worthwhile but that intensive program planning was necessary for maximum conference accomplishment. The desirability of inviting young promising investigators to such conferences was stressed.

Study Section B is also concerned with the widespread utilization of certain personality scales which, while purporting to measure specific variables, in actuality measure a broader spectrum. A conference on this is viewed as a possible Study Section contribution to the planning of better research.

Metabolism

In addition to reviewing and making recommendations on grant applications, activities of the Metabolism Study Section during 1963 centered in two areas:

A conference, entitled "Small Blood Vessel Involvement in Diabetes Mellitus," originally stimulated by the Study Section and funded by NHI and NIAMD, was held in March at Airlie House, Warrenton, Va. Proceedings have been prepared for publication.

The Study Section has maintained a continued interest in the lipid distribution program, originally stimulated by the Study Section and now funded and administered by NHI. The Study Section is currently considering, still on an informal basis, the need for providing certain other standard preparations such as mucopolysaccharides, certain sterols and certain phospholipids to qualified investigators on the same general basis as the fatty acid methyl esters are now being provided through the lipid distribution program.

Neurology A and B

Programmed activities of the two Neurology Study Sections, A and B, continue to be a joint project. Although one Executive Secretary serves for any one program and is solely responsible for its organization, the other cooperates and actively participates in the deliberations of the subcommittee concerned.

The Steering Committee on Neuroanatomy held five separate meetings beginning in December, 1962, in various parts of the country. The outcome of these deliberations was the implementation in January 1964, of a Visiting Scientist Program in Neuroanatomy, supported by NINDB. The program is aimed to attract young scientists to neurology, specifically neuroanatomy, so production of teachers and investigators in this discipline may be increased.

The procedure calls for direct contacts with the potential graduate students in the nation's colleges by visiting scientists who are well versed in the morphology of the nervous system and who have recognized reputations as teachers and investigators. The visiting scientist spends a few days on the campus to give formal and informal lectures, seminars and conferences, demonstrate the use of equipment in experimental procedures,serve as consultants to the students and teachers to discuss their research and teaching problems and to familiarize the undergraduates with training programs and career opportunities in the neurological sciences.

The program is organized on a basis of six geographical regions, under the supervision of a regional director who is an established neuroanatomist. The overall program director is responsible for organization and administration of the total national program in accordance with criteria adapted by the Steering Committee.

A preliminary survey of 70 colleges, each not exceeding an enrollment of 2,000 students, revealed 90 percent acceptance of the program. Reviewers consider this project a realistic attempt to reach the source of biological scientists of the future and the plan, a workable one. The Steering Committee plans to meet at least three times a year to keep up with the progress of the Visiting Scientist Program which will be supplemented and further strengthened by workshops.

The newly organized Committee on Clinical Investigation (Oct. 1963) aims to help identify and resolve the basic problems facing the clinical investigators in regard to obtaining PHS support in general; to specifically study and identify the bases for the recommendations of the Study Section for both the approved and the disapproved applications submitted in the past year; and to study further and consider constructive proposals to help resolve the problems so identified. The first meeting of the Committee was held Dec. 7, 1963, at New York City in conjunction with the meeting of the Association for Research in Nervous and Mental Disease.

Discussion of the many problems involving grantee institutions and medical schools were continued at the Committee's meeting in January 1964, and the following conclusions were reached: (1) Applications for clinical investigation are probably not falling off in number as the administrative staff originally believed since they may have been absorbed by other NIH programs, i.e., clinical centers, general research support, program projects, cooperative and collaborative clinical studies. (2) the 51 percent rate of approval for the so-called clinical applications is as good, if not better, than that for the overall 50 percent average for NIH grants. (This is based on a sample of 35 clinical applications reviewed by the two Neurology Study Sections.)

A brief statistical analysis of factors concerned in evaluation of PHS applications for research projects, which were rated in 35 clinical applications (15 approved and 20 disapproved) revealed the following tentative conclusions:

a) Two factors apparently of special significance in writing a

good project are: (1) adequacy in methodology and techniques and (2) adequate basic research experience of the investigator.

b) Lowest ratings for the disapproved applications occurred on experimental design and methodology and techniques.

c) Lowest ratings for the approved applications occurred on research promise of the investigator and experimental design.

d) Clinical experience of the investigator and quantity of his publications do not seem to be big factors in the approval of the applications since they do not appear to differ significantly in either the approved or disapproved applications.

The Committee did not feel that an educational program is warranted at present although a combined teaching symposium and workshop on experimental design, etc., was suggested by the Executive Secretary and proposed by the Chairman.

The Committee's findings have helped focus attention on the problems of clinical investigations and the continued need for PHS support of clinically applied research in neurology and the neurological sciences.

As true for all the programmed activities of the Neurology A and B Study Sections, the Encephalitis Panel also has joint membership from both Study Sections. One meeting held in New York City was attended by the Executive Secretary of Neurology A in March 1963.

Although the Committee on Cerebro-vascular Research has been in existence about one year, organized activities will depend on results of several conferences, symposia and meetings scheduled in the Spring of 1964.

Neurology A Study Section held its first meeting in January 1963.

For the calendar year 1963, the Study Section reviewed 174 applications, 22 of which were project site visits, and 6 were deferred for additional information.

Three foreign project site visits authorized by DRG in the summer of 1963 were accomplished by a member of the Study Section who was making independent trips to the European countries concerned. The visits were made in collaboration with various personnel of OIR, NIH, located abroad.

Nursing Research

The Study Section, working in close collaboration with the Division of Nursing, has planned a number of projects which are designed to strengthen research in the field of nursing. The Study Section has specified the kinds of additional information it needs in order to evaluate applications for support of projects for developing the research potential of faculties of

collegiate schools of nursing.

One of the first two such projects was visited by the entire Study Section in conjunction with its April meeting. Many faculty members were found to be engaged in investigation of varying degrees of sophistication, and the intellectual ferment this is creating appeared to be infecting the students.

Assistance is being given to the Division of Nursing in planning a meeting of the directors of these projects for the purpose of stimulating communication between them regarding new methods of developing research competence and other matters of mutual concern.

A discussion of methods of developing a research climate in collegiate schools of nursing and the conditions necessary for the success of efforts of this kind was scheduled by the Council on Baccalaureate and Higher Degree Programs, of the National League for Nursing, for its Spring meeting. This program was based on plans outlined by the Study Section and transmitted by a member who is on the program committee of the Council.

In order to publicize the opportunities which nursing research offers to scientifically gifted young women, the Study Section currently is seeking a donor for one substantial annual research fellowship which would be awarded on a highly competitive annual basis. A brochure describing the opportunities and the educational preparation required also has been recommended.

The Study Section reviewed 63 applications, and approved 27 (43 percent) for which the average priority assigned was 264. Last year's figures were 41 applications reviewed and 22 approved. Seventeen applications were visited before the Study Section meeting at which they first were reviewed; thirteen others were deferred for visits.

Nutrition

The Nutrition Study Section reviews research grant applications in the areas of experimental and applied nutrition involving humans, animals, microorganisms and plants.

During 1963, the Study Section reviewed 231 applications of which 146 were recommended for approval, and made 16 project site visits.

Interests of the group have included programs in international research and body composition. Liaison continues with the Food and Nutrition Board of the National Academy of Sciences and with the Interdepartmental Committee on Nutrition for National Defense.

Members of the Study Section are serving as President and President-elect of the American Institute of Nutrition.

Pharmacology and Experimental Therapeutics

The Pharmacology and Experimental Therapeutics Study Section reviewed 284 applications during 1963, and recommended 181 for approval.

Study Section members participated in activities of the Inter-Study Section Committee which organized the conference, "Evaluation and Mechanisms of Drug Toxicity," held in New York City in March of 1964.

There has been an increase in the number of applications and in the amount of funds sought for screening chemicals and plant extracts as potential drugs. These represent a different type of support in that some investigators have offered to set up indiscriminate screening procedures to screen any and all compounds that they might receive, and the Study Section could not recommend them for approval.

In order to continue to maintain high standards of review, a subcommittee was formed to meet with various members of the Medicinal Chemistry Study Sections to reexamine guidelines for support of screening applications.

The conclusion of this meeting was that, in order to merit approval, applications on synthesis of organic chemicals, those on preparation of plant extracts, and those concerned with the screening of such compounds: 1) should have strong biological implications; and 2) offer quality evaluation of biological effects rather than indiscriminate screening.

Physiology

The Physiology Study Section reviewed 300 research grant applications during 1963. Of these, 193 (64.3 percent) were approved, 85 (28.3 percent) were disapproved, and 22 (7.3 percent) were deferred for project site visits or additional information.

In connection with the review process, 18 project site visits were conducted.

The review of applications was the only formal activity during the year, but there was discussion of such problems as the effect of the published regulations of the PHS on research activities.

Dr. Donald E. Gregg, a member of the Study Section, received the Research Award of the American Heart Association in October.

Primate Research

Research proposals reviewed by the Primate Research Study Section have the use of the primate as an experimental animal as their primary objective.

The types of applications reviewed in 1963 were: (1) supplements to operational grants in support of established Regional Primate Centers; (2) operation of primate colonies; (3) establishment and maintenance of breeding colonies; and (4) field, behavioral and social studies of primates.

During 1963, 34 applications were reviewed. Of the total, 20 were recommended for approval, 11 for disapproval, and 3 for deferral. Study Section members made a total of six project site visits during the year, and

reviewed two ad hoc and one special research grant applications.

The Study Section continued its program of certification of need for rhesus monkeys imported from India. During the calendar year 1963, a total of 330 certificates were validated authorizing procurement of approximately 51,730 monkeys to be used for medical research or production of biologics. Certificates were issued to "end users" at 105 different institutions.

Psychopharmacology

During 1963, the Psychopharmacology Study Section reviewed 216 applications compared with 228 in 1962. The approval rate in 1963 was higher than that in 1962. In 1963, approximately 55 percent of the applications were recommended for approval, while in 1962 the percentage was 44.

Surgery A and B

Surgery Study Sections A and B reviewed 404 applications during 1963. Of the total, 188 were recommended for approval, 201 for disapproval, and 15 for deferral.

The two Surgery Study Sections have continued their efforts to evaluate needs and encourage a broader base of support for training grants in surgery. Toward this end a new committee was formed by NIGMS to advise on its program of training grants in the fields of surgery, radiology and anesthesiology.

The Surgery Study Sections also developed plans for a conference on Aseptic Necrosis of the Femoral Head, held in St. Louis, Mo., January 8 and 9, 1964. The purpose of the conference was to determine whether current approaches to the problem of aseptic necrosis merit the present level of NIH research grant support, and to determine what other approaches might be explored. NIAMD provided financial support for the conference through a grant to Washington University.

A joint meeting of representatives of the Bacteriology and Mycology Study Section and Surgery Study Sections was held at NIH in March 1963, to discuss the need for further research on the problem of post-surgical infections.

A new area of interest among surgeons is the potential use of hyperbaric oxygenation in clinical medicine, particularly with respect to the treatment of shock, cerebrovascular disease and anaerobic infections. As a result of this interest, an increasing number of applications in this area is being reviewed by the two Surgery Study Sections.

Toxicology

The Toxicology Study Section continued to grow in size and responsibilities during 1963. The reaction anticipated from recent publications and the press concerning the potential dangers involved in environmental contamination by pesticides, is becoming more and more evident as research interest

in these fields expands. The membership of this committee has been, and will continue to be, adjusted to meet the needs of these rapidly changing toxicological activities.

The Study Section has expanded its interest in the broad field of environmental health. The Inter-Study Section group, composed of members of the Toxicology, Pharmacology and Experimental Therapeutics, and Human Embryology and Development Study Sections, drew up plans and submitted an application for a conference on "Evaluation and Mechanisms of Drug Toxicity," as a joint effort recommended for approval by the National Advisory Health Council and held March 5-7, 1964 at the New York Academy of Sciences. Another joint effort is being planned by a committee drawn from the Toxicology and the Environmental Science and Engineering Study Sections for a "Conference on Agricultural Chemicals" to be held at Davis, Calif. early in October of 1964.

The Toxicology Study Section held its September meeting at Portland, Oreg., where members visited the University of Oregon Medical School and the nearby Primate Center at Beaverton. Following this a majority attended the "Third Symposium on Foods: Proteins and Their Reactions," at Oregon State University in Corvallis.

Members of this advisory group continue to participate in the meetings of the Food Protection Committee of the National Academy of Sciences, National Research Council. Dr. John C. Ayres, a member of the Toxicology Study Section, led a Symposium on "Problems in Food Microbiology" at the Committee's December meeting.

The Food Protection Committee has officially endorsed the program for the symposium on agricultural chemicals to be held at Davis.

Two members of the Study Section were designated to attend and compile a report on the "International Symposium on Mycotoxins in Foodstuffs" (EF 00554) March 17-18, 1964, at Massachusetts Institute of Technology.

On September 1, 1963, Dr. John E. Lane, Sr. Scientist (R) USPHS, assumed the duties of Executive Secretary of the Study Section. He attended the September 1-2 meeting as an observer and took over his new responsibilities immediately afterward.

During 1963 the Toxicology Study Section reviewed 115 applications and recommended approval of 74, or 65 percent.

Tropical Medicine and Parasitology

Activities of the Tropical Medicine and Parasitology Study Section during 1963 reflected continued interest in encouraging better oriented, more inclusive interdisciplinary research in all fields of medicine in the tropics.

Many of the applications considered were for research projects being conducted in the temperate and frigid zones, as well as the tropics. There was an appreciable increase in interest on the part of scientists from Central

and South America, with a resulting increase in the number of applications from the Latin American countries.

The number of applications considered by the Study Section has continued to increase. The total was 303 for 1963. Of these, 188 (58 percent) were approved. With the continued increase in workload, a division of the present Study Section into two sections is being considered.

Visits were made to 34 projects in the United States, Argentina, and Brazil. Staff personnel from DIR participated in seven of these visits.

Members of the Study Section have continued to participate in national and international scientific organizations and to be recognized for their contributions to science. These include: Dr. Edward A. Steinhaus, appointed Dean of the Division of Biological Sciences of the University of California at Irvine, and elected President of the Entomological Society of America; and Dr. J. Linsley Gressitt, named the first recipient of the Linus Allen Bishop Distinguished Chair of Zoology of the Bernice P. Bishop Museum in Honolulu.

Dr. Ernestine B. Thurman, Executive Secretary of the Study Section, was elected National President of Sigma Delta Epsilon, a graduate women's scientific fraternity. She also served on the planning committee for the XVI International Congress on Zoology.

As is the custom in this Study Section, new members were provided orientation the day preceding the September Study Section meeting. Observers from DRG, other divisions and institutes of NIH, and BSS attended the orientation meeting.

During the year, there were 34 observers who attended the three meetings, many of whom were being oriented into the extramural research program.

Virology and Rickettsiology

In addition to its review of research grant applications, the Virology and Rickettsiology Study Section attempts to stimulate investigations to enable systematic research on the biology of, and the disease or tumor production by, viruses and rickettsiae. Both basic research on the role of cell or viral constitutents, such as nucleus protein (DNA, RNA, etc.), and the study of categorical diseases are matters of concern.

Requests for support to study the role of viruses as related to cancer continues to increase. Efforts to apply and to develop new scientific information received more emphasis during the year. Investigations on the causation of the common diseases, such as upper respiratory, enteric or childhood diseases, as well as on vaccines to protect population groups, are continuing. Interest is growing also in the role of viral infections in congenital anomalies and neurological conditions.

Steady progress is being made in basic studies of viruses in cancer causation and in development of better methods of study. The ability of human

viruses to experimentally produce tumors in laboratory animals has been confirmed. Studies seeking evidence of similar relationships in human populations are being supported. Important advances are being made in study of micromolecular structures of viruses and of cells as they relate to diseases as well as to cancer. An increased attention to the study of greater practical application of research findings, as in the diagnosis, treatment and recognition in the field by health agencies, is anticipated.

A total of 285 applications were reviewed during the year, of which 59 percent or 168, were approved; 34 percent or 99 were disapproved; and 6 percent or 18 were project sites visited to obtain additional information. Infectious disease oriented proposals numbered 173; cancer, 93; and others, 19.

Financial support was provided for two large conferences. These were the International Symposium on Newcastles Disease Virus As An Evolving Pathogen, at the University of Wisconsin, July 15-17, 1963; and the 17th Annual Symposium on Fundamental Cancer Research at the M. D. Anderson Hospital and Tumor Institute of Houston, Texas, February 28-March 2, 1963. Both of these meetings served a very useful function in placing related research in proper perspective and outlining goals for the future.

Recent upsurge of interest in the study of both viral diseases and of viruses in cancer has resulted in the formation of numerous advisory panels elsewhere within NIH. Continued liaison will be maintained with such groups which provide overall perusal of research activity in the various areas, as well as facilitation of programmed research on specific virus problems needing investigations.

Visual Sciences

During 1963, the Visual Sciences Study Section reviewed a total of 169 research grant applications. It recommended approval for 106, disapproval for 46 and deferral for 17.

The Study Section continues to be active in planning conferences. Two applications were submitted and approved during 1963, the first for a symposium on "The Physiological Basis for Form Discrimination" held in Providence, R. I. January 23-24, 1964; and the second for a "Symposium on the Lens" to be held in Minneapolis, Minn. in December, 1964.

Plans are continuing for conferences on the Vascular System of the Eye and on Differences in Inflammatory Reactions in Vascular and Avascular Tissues.

A subcommittee has been appointed to begin planning a second conference on vision, this one to be concerned with abnormalities of binocular vision.

STATISTICS AND ANALYSIS BRANCH

Office of the Chief

Administration

Organizational changes within DRG during 1963 significantly affected the Statistics and Analysis Branch. Effective June 17, 1963, Mr. Peyton Stapp, Chief of the Program Analysis and Statistics Branch of the Office of Program Planning, OD, was named as an Assistant Chief in the Division to develop DRG's data processing and statistical operations. Toward this end the following DRG units were placed under his direct supervision:

1. Data processing activities of the Research Grants Review Branch
2. Records and Reports Section, CDRB
3. Statistics and Analysis Branch, DRG
4. Research Documentation Section, OC
5. The Grantee Institution Profile Study, OC

Plans called for the integration of the statistical analysis and data processing functions of DRG and of the Office of Program Planning, OD. The pertinent Sections in OD were the Design and Analysis Section and the Operating Statistics Section. The first step in this direction was accomplished in the fall of 1963 by bringing together all units to be coordinated into one location in the Westwood Building. Following this, activities were combined and consolidated in a Statistics and Analysis Branch with four sections. These include:

1. Data Processing Section
2. Statistical Surveys Section
3. Operating Statistics and Reports Section
4. Research Documentation Section

This report presents the projects completed, currently in progress, and planned in the several sections of the Branch from January 1963 through June 1964.

Automatic Data Processing Study Team

General: The Automatic Data Processing Study Team was transferred to DRG from the Management Policy Branch in recognition of the primary responsibility of DRG for developing and installing a central data system integrated with the data systems of the institutes and divisions. The first phase of a computerized system, called Pending Research Grant Applications (PRGA), as developed by the study team, is now producing pink sheets with basic data ready for the addition of text, work sheets, resumes, and statistical reports for the preliminary review groups, such as study sections; and priority listings, investigator listings, and resumes, for councils. The completion of this phase is scheduled for July with the production by the computer of the Notice of Research Grant Award from the control record. The activities of the team from the time of transfer to June 30, 1964 are described below.

Operating Statistics and Reports Section

Recurring Reports

Status of Programs and Resources of NIH: This handbook, reflecting the status of programs and resources of NIH, is compiled, edited and updated by the Operating Statistics and Reports Section. The handbook currently consists of approximately 44 tables and charts which depcit the trend and current status of NIH programs.

Basic Data Relating to the NIH: Data for this pocket-size reference book, commonly referred to as the Basic Data Book are collected and compiled by OSS. The 1963 edition contained 24 tables and charts; and 1964 book published in February 1964, contained 35 tables and charts. The contents of the Basic Data Book will continue to be modified from year to year in an effort to make it a more useful, ready reference document.

National Science Foundation Federal Funds for Science Survey: Data for the NIH portion of the survey are compiled annually for the NSF by this Section. Composed of 16 tables, the NIH report presents data on the research activities in NIH by performer, field of science, etc.

Office of Education Federal Funds for Education Survey: The responsibility for the compilation of this biennial report (to become an annual report commencing in 1964) was assigned to the OSS in 1963. The report consists of detailed and comprehensive data relating to the NIH extramural training activities. The 1961 OE report consisted of 90 "component" parts and the 1963 report completed in April 1964, consisted of approximately 1,000 such parts, each part representing a detailed report of a segment of the NIH training program.

Surgeon General's Highlight Reports: Beginning in June 1963, OSS was given the responsibility for the preparation of the consolidated statistical portion of the Surgeon General's Highlight Report. Prepared after each Advisory Council meeting, the report summarizes the Council actions on research grant and training grant applications reviewed. Individual reports, prepared by the institutes and divisions according to instructions and format prepared by OSS are consolidated by OSS into a single five-page document distributed to the Surgeon General, throughout NIH, and interested agencies. In March 1964, the individual institute reports were prepared successfully by the computer on a trial basis and it is anticipated that this method will be used in the future.

Non-recurring Reports

Special Reports: Most requests for statistical data relating to the NIH programs are coordinated by OSS. These requests for data which originate primarily outside NIH, come from members of Congress, congressional investigating committees, special investigating committees, DHEW, Office of the Surgeon General, etc. Approximately 50 reports responding to special requests of this nature were prepared during the past 18 months.

Status at Beginning of Year: Early in calendar year 1963, the paper tape-to-card conversion was beginning to function efficiently and the programmers were testing the update and report routines. A trial run was made, parallel with the manual system, during the February/March Council meetings.

June Council Meetings: During the June cycle, the computer system ran solo for the DRG preliminary review groups; that is, the study sections actually used the work sheets, pink sheets, and resumes produced from the system. Institutes used the listings as checks against their own records and for other internal operating purposes.

In late summer, a rather extensive redesign of the institute reports was undertaken in an attempt to make the printouts more readable. These changes were programmed, tested, and ready for use by March 1964.

November and March Council Meetings: These meetings went very well. A few institutes used some of the computer listings for their council meetings.

Future Plans: It is expected that a system similar to the Pending Research Grant Applications (PRGA) will be developed for training grant applications in the future.

Special Reports

Scientific and Technical Communications, DRG: A report was prepared describing the information activities in DRG. These were classified according to three types of information - scientific, descriptive and administrative.

Effectivenss of Selection Procedures Used in the Research Grant Programs, NIH: Priority scores were examined in an exploratory, retrospective study as an indication of the effectiveness of the selection procedures used in NIH for the support of research extramurally. Reported findings included in the NIH Report to the Surgeon General of the Developments of the Week, were used as an index to successful grant supported research projects. The results indicated proposals assigned good priority scores were more likely to be successful or productive than those with poor priority score. Proposals assigned poor priority scores were those with unknown risk, the majority of which were those with unknown risk, the majority of which were found to be assigned better priority values at the time progress was reviewed indicating that their potential for success was recognized as more information became available.

Data Processing Section

General: The Data Processing Section was initially organized with a Document Control Unit (PRGA, Verification and Machine Operations) and a Records and Reports. In January 1964, the functions of the Statistical Processing Section were absorbed by the Data Processing Section which was then tentatively reorganized with an internal organization patterned along functional lines.

The Section, as a whole, continued from the time of its initial organization to discharge the functions incumbent upon a central repository of statistical information concerning the extramural research and training support provided by NIH. Most significantly, it was deeply involved in, and firmly committed to, a fully integrated and virtually completely automated operation of the DRG grants system. The scope of activities in which this section is engaged can best be appreciated by a review of the work being performed by each of its component units.

Document Control Unit: This unit controls the data processing system for competing research grant applications from the initial receipt of the application in DPS through the review process, and ultimate award or disapproval. The Pending Research Grant Applications (PRGA) system became operational during this year and, although modification and improvements continue, is functioning in a routine fashion.

Documentation Unit: A key organization in making possible the orderly and successful transition to the new PRGA system is the Documentation Unit. Extensive effort has and continues to be expended to complete the information in the Active Research Grant (ARG) file and in the file transferred from PRGA so that these files are adequate for present report requirements and for the Type 5 renewal procedure. This involved, in addition to the normal routine coding, the caputre of such data as department title and future committed funds, by year, on some 13,000 active research grants.

Programming Unit: The PRGA-ARG Transfer routine was made operational and PRGA data from the June 1963, November 1963, and March 1964 purges were put into ARG formats. These data have been the input for several special reports routines. Routines have also been written for the movement of grant records from the ARG to the History file.

Systems Development Unit: In preparation for the integrated operation of the DRG grants system, the Renewal Notice cycle specifications were written and released to the programmers. Specifications were also written in conjunction with the Study Team on the PRGA-ARG Transfer routine and released to the programmers. Present effort is directed toward written procedures for the use of the operational groups when handling Type 2 and Type 5 applications in the integrated system.

Working with data collected by the Grants Management Branch, a new file is being established on each grantee organization, and the O&G numbers and the Financial Management Branch account numbers are being reviewed to remove unnecessary duplications. The resultant file will be used for addressing Type 5 renewal notices and the notices of awards.

Machine Unit: The normal heavy file maintenance and reports work of this unit was made even greater by a large amount of punching for the Grants Management Branch in connection with the institution file and the additional data required for the new integrated system.

Reports Analysis Unit: This unit coordinates the section's efforts in assembling information for reports on the extramural research grant programs of NIH and/or PHS, the annual publications as well as the monthly news release. By October 1963, fiscal year 1963 publications (except Parts II and V) were completed. The extramural data processing programs needed for these publications were carried out by the George Washington University contract personnel.

During the past six months, the Unit's efforts were devoted to Book II, 1963 and Book V, 1962 of the annual publications series, as well as to assembling varied reports requested by NIH personnel and other sources, both Congressional and Executive.

Records and Reports Unit: On December 1, 1963 the Records and Reports Unit, formerly the Records and Reports Section of the Career Development and Review Branch, began capturing data for training programs on a mechanized record and has continued as the Central Data Storage and Retrieval System for the PHS Training Programs. The system has been expanded to include the Trainee Status Report. This report stems from a system which has been developed to issue annually to each program director who receives a grant, a listing by name of each trainee he has reported and dates of each appointment period for a given grant year. The program director is required to review the list, answering the questions asked relating to each trainee's level of accomplishment, and update it with names of trainees appointed but not yet reported. The Trainee Status Report will assure a tighter control of the trainees appointed, thereby making reliable data available within a reasonable period of time after termination of the respective grant years.

Annual reports were prepared on the Fiscal Year 1963 Research Career Program Award and Regular and International Fellowship Award Programs. The two reports include detailed information on each awardee or fellow, and tables consisting of number of applications received and the subsequent institute actions including awarded funds.

Extensive reporting was accomplished for the Office of Education which covered Fiscal Years 1961, 1962 and 1963 grant awards made in the NIH and BSS Environmental Health Training Programs.

In addition to special and routine reports for NIH or BSS offices, congressional inquiries and other organizations, the unit expended extensive effort in preparing material for the Fountain and Wooldridge Committees. In connection with a Fountain Committee request, a major effort was mounted to code expenditure reports for FY 1961 and FY 1962. This represents the first attempt at the mechanical processing of expenditure report data.

Data Processing Section

In January 1964, the functions of the former Statistical Processing Section were absorbed by this Section. This coordination of functions was accomplished in order to make possible the development and availability of a single source of statistical information for activities located in selected divisions of the PHS.

In March 1964, the individual institute reports were prepared successfully by the computer on a trial basis and it is anticipated that this method will be used in the future.

Internal Reports and Analyses: A considerable amount of the Section's effort goes into the preparation of responses to requests for information initiated by top management within NIH, relating to either the intra- or extramural programs. The requests may be made for (a) obtaining data concerning some program or activitiy where previous information is not readily available, (b) reviewing a specific area for purposes of providing data sufficient to evaluate current policy, or (c) assembling information basic to the establishment of new policy. An Analysis of the Changing Pattern of Research Grant Programs consisting of 35 pages of tables, charts and interpretations prepared in 1963 is an example of a response to one such request.

Statistical Surveys

Distribution of PHS Awards in Selected Institutions by Program, FY 1962: Two reports were prepared showing summaries of distributions by institute, type of grant program, type of construction program and other detail for nine grantee institutions in one report and 10 in the other. In the latter, the distribution of awards is snown by divisions and departments of the institutions selected.

The Research Contract and Related Documents as a Source of Statistical Information: Analyses were made for administrative purposes to determine the nature and extent of statistical data contained in documents relating to NIH research supported through contractual procedures.

Organization of Grantee Institutions: A plan is being devised for a system of information retrieval for the distribution of NIH grants in the organizational hierarachy of institutions. Charts for the major institutions involved in NIH-sponsored research and training are being collected and organized. The availability of organizational hierarchies of divisions and subdivisions within grantee institutions will make feasible the retrieval of logical and consistent information for the administrative, scientific, and physical location of NIH awards in these institutions.

Analysis of Results of the Survey of Personnel Working on NIH Research Grants: This survey is an attempt to probe the attributes and characterisitcs of all participants on a sample of NIH Research Grants which were active during fiscal year 1963. Analysis pertaining to different population groups has been completed from time and income, demographic characteristics educational background, present educational experience, site of research, position on research project, and percent of time spent on different activities. Work is proceeding on analysis of data relating to the major field(s) of study relating to academic degree(s) held by research grant personnel and major field(s) of study for student personnel, as well as the major field(s) or specialities of present research or scientific interest.

NIH Extramural Program Awards by Type and Control of Sponsoring Institution: Compilations by NIH extramural program and State for each fiscal year 1954, 1959, 1960, 1961, 1962 have been made to show number of sponsoring institutions, number of grants, and dollars awarded according to four categories of institution: higher education; hospitals which are independently owned (not owned by a parent institution of an educational or medical research category); government; and a miscellaneous grouping including research institutes or laboratories, societies, or organizations, associations, outpatient clinics, or foundations. Tables also summarize dollar amounts in each category according to public or private control of the sponsoring institution. Graphic illustrations from this material show NIH extramural program trends 1954-1962.

Trends in Priority Scores Assigned to a Sample of Principal Investigators with Low Priority Ratings During the Period 1951-58: This study shows the trend of research grant experience of a sample of 100 principal investigators selected from those whose proposals submitted during the period of 1951-58 were assigned a low priority score by study section. Several alternative approaches to the analysis are: (1) comparison of the total research proposal experience during the period in regard to priority scores and approval rates, (2) comparison of the experience before and after the low priority score falling in the sample, and (3) an analysis of the research grant experience in two different time periods, 1951-56 and 1957-63.

Recommendation for Approval and Disapproval and Priority Score Information for Competing Applications from Principal Investigators Sponsored by 302 Institutions of Higher Education in the United States and Possessions, Fiscal Year 1960: Data have been drawn from SPS, DRG statistical data cards of May 1960, revised January 1961. Priority scores fro the more than 3,900 "approvals" are analyzed by State and geographic division as well as by dollar amount requested per application.

Analysis of Research Grant Applications Reviewed by Study Sections in January-February 1961 with Respect to Information of a Nonscientific Nature Which May Influence the Direction of a Recommendation for Approval or Disapproval or the Level of a Priority Rating: Common denominators are being sought from 2,959 applications with regard to such matters as amount of support requested, characteristics of the principal and co-principal investigators, and type of sponsoring institution.

Project Control, NIH: This function, which was termed Reports Control, prior to January 1962, was a responsibility of the Section until January 1964 at which time it was transferred to the Office of Program Planning, OD.

Research Documentation Section

Research Grants Index: In May 1963, the Section published its second annual Research Grants Index (PHS Publ. 929). This 1,450-page volume is a scientific subject-matter analysis of approximately 15,000 research projects supported by PHS during fiscal year 1963. Approximately 10,000 copies of the Research Grants Index were distributed to administrative personnel, grant -

supported investigators and other scientists, and scientific institutions in this country and abroad.

This Index contains 814 pages of information classified under nearly 9,000 main subject headings and subheadings, alphabetically arranged. The remainder of the volume is divided into three appendices. Appendix I is a numerical listing of grant numbers with names, addresses and recent publications of investigators conducting PHS grant supported research projects. Appendix II is an alphabetical listing of both principal and co-investigators. Appendix III is a categorization of research grant projects into 40 broad research areas, such as cell biology, communicative sciences, radiation, etc. The volume is prepared for publication from sequential camera cards which are phtoographed to produce film copy. Consideration is being given to the possibility of transferring to computer techniques in the future.

In April 1964, the Section published its third annual Research Grants Index (PHS Publ. 925) in two volumes, totalling 1,752 pages, to provide detailed information on the scientific content of the nearly 16,000 investigations given PHS grant-in-aid support during fiscal year 1963.

Volume I of the Index contains 958 pages of information on research programs in the medical, dental and allied health fields, classified alphabetically under 6,391 main headings and 21,017 subheadings. Volume II is divided into three apeendices. Appendix I is a numerical listing of grant numbers with names, addresses and recent publications of grantees. Appendix II is a categorization of grants according to approximately 60 general research areas such as, surgery, tropical medicine, and toxicology. Appendix III is an alphabetical list of principal and co-investigators.

Nearly 10,000 copies of the Index were distributed to Federal administrative personnel, and to PHS grantees and other scientists in this country and abroad.

NIH Intramural Index: During 1963, the Section also produced an index of NIH intramural projects. In conjunction with the Research Grants Index, this gives a complete guide to NIH supported research.

Medical and Health Related Sciences Thesaurus (PHS Publ. 1031): In March 1963, the Section published the Medical and Health Related Sciences Thesaurus which is now being revised. This publication is a dictionary of approximately 12,200 scientific terms and 9,000 cross references. It is maintained on a computer and was compiled as an indexing guide in connection with the preparation of the Research Grants Index. In establishing terminology for the Thesaurus, effort was directed toward compatibility with similar existing compilations, particularly the Medical Subject Headings of the National Library of Medicine. Nearly 1,500 copies of the Medical and Health Related Sciences Thesaurus have been distributed, mostly in response to individual requests. In addition, copies of the Thesaurus tape have been furnished upon request to aid individuals engaged in computer research methods of building medical thesauri.

Extractions from the Research Grants Index: Two additional publications were extracted from the Research Grants Index during fiscal 1963. A separate compilation was made of the foreign grants and another of the research projects administered by NIGMS. These publications were prepared by photo-offset reproduction from sequential camera cards.

Statistical Summary of the Research Grants Index: The first Statistical Summary of the Research Grants Index was prepared in response to suggestions made by NIH scientist-administrators who have used previous editions of the Index as an aid in scientific evaluation of PHS extramural programs. This Summary is a 324-page internal report which recapitulates the data contained in pages 1-957 of the Index. As in the latter volume, the Summary contains approximately 6,400 main subject headings, 2,000 subheadings, 10,000 cross-references and 2,700 "see" terms which refer to the scientific content of the grant-in-aid programs. Under each main heading and subheading in the Statistical Summary, however, the total numbers of projects for each institute or division are shown instead of the individual grant numbers and descriptive indexing items which appear in the Index.

CAREER DEVELOPMENT REVIEW BRANCH

Origin and Functions

The CDRB has operated since March 1961 as the coordinating unit for all NIH extramural training award programs. This responsibility has since been extended to include the programs of the PHS Bureau of State Services. CDRB functions include:

(1) Review of applications for predoctoral, postdoctoral and special fellowships, graduate training grants, and research career program awards for acceptability and assignment to the appropriate Institute; (2) scientific review and evaluation of the above types of fellowship applications through committees of academic research scientists, with staff assistance to these committees; (3) development and implementation of uniform policies and procedures for central management of training award programs; (4) capture and storage of data on applications and awards in the programs for which CDRB has a coordinating responsibility, and in the international postdoctoral fellowship, direct traineeship, undergraduate training grant, postsophomore fellowship, and student part-time research fellowship programs; (5) periodic analyses of current professional activities of former fellows and trainees and other studies important to health research training.

Increased Scope of Administrative Responsibilities

In 1963, the Branch was reorganized to enable an Assistant Branch Chief to administer each of the three programs of the Branch: Fellowships, Research Career Program and Training Grants. Three new positions were created to provide each Assistant Chief with a program management specialist.

Three Coordination Sections and an Assignment Section were established as separate entities within the Branch. These serve as the point of reception, assignment, and distribution to the institutes of virtually all applications for fellowships, research career awards and training grants. Also, the Records and Reports Section of CDRB was transferred to the Statistics and Analysis Branch of DRG.

New Levels Set for Stipends

A comprehensive study of stipends paid to fellows and trainees was carried out during 1963. Approximately 30 staff members of the institutes, DRG, and OD participated in visits to over 200 deans and department heads in 34 universities and three hospitals. Of major interest was the opinion of university personnel relevant to the adequacy of stipends, dependents' allowances, supplementation and the need for uniformity of stipends between fellows and trainees. One of the major results of the stipend survey was the decision to raise predoctoral fellowship stipends by $600 as of July 1, 1964. Thus, the new levels will be: first year, $2,400; intermediate years, $2,600; and terminal year, $2,800.

Several meetings and symposia were attended by the professional staff in addition to their regular visits to colleges, universities and other research organizations in an effort to become more familiar with present research facilities and training and to impart information concerning PHS training programs. For example, three fellowship review panels met in Minneapolis in July 1963, with faculty and administrative officers of the medical and graduate schools of the University of Minnesota to explore the philosophies behind the Ph.D. program in clinical fields at the University.

Record Year Indicated for Fellowships Program

In calendar year 1963, a total of 3,448 applications for fellowships, including new and competing continuations, were reviewed by the 12 scientific extramural panels, a slight increase over the 3,358 applications reviewed during 1962. In the spring series of panel meetings in 1964, a record 1,690 applications were reviewed.

In September 1963, the Fellowships Coordination Section was established directly under the Assistant Chief for Fellowships. All fellowship applications arriving at NIH, including continuation requests, are channeled through this Section for preliminary processing. From January 1, 1963, to March 31, 1964, the Coordination Section processed 1,918 continuation applications of all types. The Section is also responsible for maintaining a fiscal control system on all expenditures connected with predoctoral fellows. This is essential in order to assure retrieval of funds due NIH as a result of premature termination of fellowships or other reasons. Since September 1963, when this responsibility was assigned to the Section, approximately $110,000 has been retrieved from various institutions.

Improvements in Terminologies and Forms

In order to eliminate any possible confusion between the Fellowships Program and the Research Grant Program the term "supply grant" has been replaced by "supply allowance," and the administrative procedure involved in applying for and awarding supply allowances has been simplified. The supply allowance is now requested on the Facilities and Commitment Statement for an initial year and on the Continuation Request for subsequent years. A new award statement has been devised specifically for this allowance.

A new procedure has been developed and put into operation to authenticate the citizenship status of non-citizens who apply for fellowships. Such individuals request the Immigration and Naturalization Service to furnish pertinent information concerning their citizenship status directly to CDRB.

Virtually all forms used in the fellowships program were revised in the spring of 1964. Improvements in the forms are to a large degree attributable to comments expressed by participating universities, the awarding institutes and divisions, and other units of PHS. In July 1963, the informational brochure describing the policies and procedures of the fellowships program was revised and widely distributed among university and PHS personnel. Due to subsequent changes in the program, a second revision of the brochure was inaugurated in the spring of 1964.

Status of PHS Fellows Surveyed

The Analysis and Evaluation Section has completed preparations for a survey, to be initiated in the fall of 1964, in order to determine how individuals who were awarded PHS fellowships have fared professionally in comparison with those individuals who applied for but did not receive PHS fellowships. The study will embrace both predoctoral fellows and trainees who acquired their degrees within the past four to six years.

In March of 1964, this Section issued a comprehensive report on the growth trends of the predoctoral, postdoctoral and special fellowship programs from fiscal year 1955 through 1963. The report indicated that, although the number of applications received by NIH increased by 308 percent during the eight years, the trend is now leveling off. The number of applications received in fiscal year 1963 was only 4.2 percent above that of the previous year. It is believed that the 1964 increase will be approximately 14 percent. Because of the heavy rise in number of individuals who will be in the age group usually seeking graduate degrees during the latter part of the 1960s, plus the expected increase in undergraduate degrees to be awarded, it is anticipated that the total number of new fellowship applications received by NIH will continue the upward trend already noted for FY 1964. Applications are projected to total approximately 9,000 by FY 1970.

Research Career Program Coordinated

A total of 1,333 applications pertinent to the Research Career Program were received in calendar year 1963. Of the 994 career development (K-3) applications, 330 were new, 532 were committed continuations, and the remainder were miscellaneous. The 339 career (K-6) applications consisted of 167 new, 23 supplementary, and 149 committed continuations. During the same period, the institutes and divisions made a total of 1,049 awards, consisting of 812 career development, 236 career and one chairman's grant.

In line with the overall Branch reorganization, the Research Career Program Coordination Section was established in September 1963, and placed under the direct administration of the Assistant Branch Chief for Research Career Program.

Considerable activity within the Office of the Assistant Chief for Research Career Program was devoted to a conference in April 1964, of representatives of each RCP awarding unit within PHS. One member of each awarding unit's RCP review committee and one extramural staff member from each unit were present. The conference was convened to consider the Program in its totality, in terms of underlying philosophy, purpose, objectives, program need, productivity and current and foreseeable problems. The subjects considered ranged over such varied but interrelated topics as disposition of professional fees; maximum salary limitation and overall problems of salary determination; priority, in terms of geographic distribution and developed, versus underdeveloped, schools; supplementation by the grantee institutions; and sharing of the award costs. The conference was most productive in that it made apparent the inherent value of the RCP as well as the need for its continuation. Furthermore, it gave to those whose responsibility it is to

advise on matters pertaining to the program, a greater comprehension of the magnitude and complexity of the many problems which must be resolved, and, to those who must make the ultimate decisions, a better supporting background.

During 1963, mutually beneficial contact was established and strengthened with the RCP awarding units. In this connection, and at the request of the awarding units, a series of meetings was conducted, and a number of memoranda and statistical tables relative to specific problems and decisions were developed and disseminated.

The Analysis and Evaluation Section of this Branch and the Records and Reports Section of the Statistics and Analysis Branch worked closely with the Office of the Assistant Chief in the development and analysis of statistical data pertinent to the RCP, and in the preparation of special and routine reports.

Career Program Extended to PHS Division of Nursing, BSS

With the assignment of Development (K-3) awards to the Division of Nursing, Bureau of State Services, in 1963, the RCP for the first time encompassed areas within the PHS, other than NIH.

An informational brochure describing the policies of the Program was distributed to university officials and PHS personnel in January 1963; a revision, incorporating subsequent program changes, is in preparation, and distribution during 1964 is anticipated.

A manual covering procedures relative to the receipt and processing of RCP applications is being developed for use within the PHS. Also in preparation is a similar manual relative to the administration of RCP awards intended for use within the grantee institutions. The RCP application was revised during 1963 to reflect recent program changes. The Notification and Statement of Award is currently undergoing a similar revision.

Receiving continuing consideration within the office of the Assistant Chief is the coordination of the assignment of RCP applications with applications for related research grants. This problem is of particular importance since the value of an RCP award to an individual awardee is markedly affected by the availability of funds to support his research. This office is investigating methods of solving this problem in collaboration with the Assignment Unit, the Research Grants Review Branch, and the individual PHS awarding units. At the same time, means are being sought to bring about a greater degree of coordination and uniformity in the overall review and awarding processes of the Research Career Program.

Training Grants Program Policies Clarified

From January 1963 through February 1964, a total of 4,379 applications for training grants were received and assigned to the institutes and certain divisions of the Bureau of State Services. Of this total, 779 were new applications; 523 were competing renewals; 601 were supplemental; 2,421 were committed continuations; and 55 were miscellaneous types.

During the same period, staff personnel of NIH and BSS collaborated in revising Part VI of the Grants Manual, which specifies the responsibilities of institutions with regard to training grant funds. It covers the grantees' accountability for equipment purchased, the use of training grant funds for alterations and renovations, the principles applicable in determining the amount of stipends to be paid to trainees, the use of training grant funds for tuition and fees, and other related matters.

A series of meetings with the Institute Training Grants Chiefs has identified several problem areas. For example, it became evident that NIH has not been acquiring the names of students being supported under a training grant within a reasonable time after activation. A procedure was established to require institutions to submit a Statement of Appointment of Trainee within a fixed period after the student reports for duty.

The Assistant Chief for Training Grants visited several medical centers in order to hold discussions with deans, business officers, program directors and other appropriate officials concerning PHS policies relating to training grants.

Analysis and Evaluation Section Activities

This Section was involved in a variety of activities in addition to those of the three foregoing programs.

A report on priority score data is compiled by this Section three times a year. It summarizes the priority scores of the panels of the Central Qualifications Board and indicates approval rates and priority scores by panel, level and institute.

This Section also cooperated with the Statistical Processing Section in updating an unduplicated list of fellows prepared in 1958. Thus, for the first time in five years there is available a complete and unduplicated list of fellows supported by all institutes from the inception of the Fellowship Program through June 30, 1961. An analysis was also undertaken to determine the status of 4,700 former Indirect Trainees two years after they completed their NIH-supported training.

GRANTS MANAGEMENT BRANCH

General Responsibilities

Activities of the Grants Management Branch related to management of the PHS programs are directly involved in the formulation and implementation of policies, procedures and practices for research projects, training grants, program projects, clinical centers, general research support, and health research facilities grants. The Branch exercises influence on all aspects of administration, exclusive of scientific consideration, of NIH and Bureau of State Services grant programs.

Scope of Activity

During the period covered by this report, the Branch placed increased emphasis on developing policies, procedures, and guides governing the administrative and fiscal management of PHS grants in the areas of direct and indirect costs, and toward implementation of the policies and procedures contained in the Grants Manual.

To facilitate the administration of the PHS grants programs, closer liaison was established with the staffs of the extramural program institutes and divisions to evaluate the effectiveness of approved grants administrative and fiscal policies and for determining the need for modification or refinement of approved policies. Operating guides and criteria were developed for the use of grantee institutions and for grants management staffs of the awarding institutes. Attention was paid to accumulating precedent actions which could be used for developing new policies, revising established policies, and for achieving consistency of interpretation of existing policies.

Special studies were conducted to gather background information relative to the effectiveness of PHS grants policies and procedures.

The Branch continued to assist the extramural program staffs of PHS in the resolution and interpretation of policy questions and assist them in answering inquiries received from grantee institutions.

Personnel Changes

Mr. Guerry R. Smith was appointed Chief of the Grants Management Branch succeeding Mr. Sidney B. Cohen who left to become business manager of Gallaudet College. Prior to his appointment, Mr. Smith was Deputy Assistant Administrator for Management of the Foreign Agriculture Service of the Department of Agriculture. Subsequent to Mr. Smith's appointment, Dr. Edward Schwartz was named Assistant Chief. Dr. Schwartz, who completed a year's training in the NIH Grants Associate Program, was formerly a supervisory research psychologist with the Veterans Administration. In addition, four grants management specialists and one grants management assistant were added to the staff.

Organizational Changes

On April 14, 1964, the Director of NIH approved the establishment of a Program and Technical Management Section within the Grants Management Branch, and the abolishment of the Financial Management Section and the Policy, Procedure, and Audit Review Section. These changes reflect the efforts of the Division to realign its management controls and provide the focus for the further development and maintenance of policy and procedural guides for the awarding institutes and divisions and grantee institutions.

Grants Management Controls

Staff members of the Branch, coordinating with representatives of the awarding institutes and divisions, the Office of the Director, NIH, and the Office of the Surgeon General gave attention to the refinement and up-dating of Part V of the Research Grants Manual, the development of policies and procedures relating to training grants for inclusion in Part VI; modification of the Notification and Statement of Grant Award (PHS form 1533) and the Report of Expenditures (PHS forms 421 and 2933), and implementation of the revised grants payment procedure.

Special reviews of grants policies and procedures were also made concerning the payments of hospitalization charges to grants as part of clinical research carried out in "discrete units" and on a "scatter beds" basis, and fringe benefits allowances.

A concerted effort was made to facilitate the receipt of overdue Reports of Expenditures. Follow-up procedures were revised and provision was made in Part V of the Manual to extend the deadline for these reports from 90 to 120 days after the termination date of grants.

Communications

(1) Recognizing that each college, hospital, institute, foundation or university has an administrative organization designed to conform to its own unique combination of staff, facilities, experience, and programs, active PHS grantees were surveyed on January 20, 1964, (NIH form 35) to seek information for the purpose of up-dating and expanding mailing lists of the PHS. Data obtained are also being used to establish institutional profiles.

(2) Monthly grants management liaison meetings were established for grants officers and assistants of each of the awarding institutes and divisions to exchange information and clarify existing grants policies and procedures. Attendance has been 60 to 70 persons per meeting.

(3) Three two-day USPHS Research Grant and Award Administration conferences were held for officials of colleges and universities to exchange information regarding PHS grants policies and procedures. Twenty-one representatives from 13 eastern colleges and universities attended the first conference in Bethesda, January 13 and 14, 1964. Forty-six

representatives from 25 eastern colleges and universities attended the second conference March 11 and 12, 1964. The third conference was co-sponsored by the University of California on the Berkeley campus, and was attended by 74 representatives from 37 western colleges and universities.

INTERNAL OPERATIONS BRANCH

The Internal Operations Branch provides administrative services for Division personnel, and furnishes program materials for the extramural programs of other divisions, institutes and bureaus of the PHS.

The Branch functions as follows:

Office of the Chief - The Office of the Chief provides overall supervision of all Branch activities, and maintains liaison with other divisions and institutes, in addition to performing specific functions, such as space planning and forms clearance control. During the past year, this office planned, scheduled and supervised the move of the entire Division from three buildings into the Westwood Building. During 1963, the Management Technician (Forms Analyst) devised and received approval on approximately 63 new forms. During this same period, 25 of the existing major program forms were revised and 34 forms declared obsolete to the needs of the Division. The volume of work originating from the processing of travel vouchers of consultants engaged by the several study sections necessitated the addition of a second bookkeeper to handle the work load. During this period, over 7,300 consultants' vouchers were processed and forwarded to the various study section chairmen for payment.

Office Services Section - This Section performs a variety of functions and duties including procurement, property, supply, equipment repair and maintenance, and documents relating to these activities. Another area of concern is the assembly and mailing of seven different major program application folders. The volume in this area has increased from 5,000 to 8,000 applications per month. This Section also wraps and mails an average of over 3,000 miscellaneous packages per month. It is also responsible for the operation and maintenance of the various office copying machines throughout the Division, and a Service Room which offers reproduction service of different types, amounting to countless thousands of copied documents.

Special Services Section - This Section is primarily concerned with providing special services such as general typing, extra clerical and typing help when needed, and control of the Flexowriters used in the general letter typing operations. During 1963, approximately 350 jobs were accomplished on the Flexowriters, ranging in size from 10 to 3,000 letters per job. Other services are the transcribing of magnetic tapes from various seminar series and recorded meetings from the various conference rooms. The Section specializes in typing manuscripts, manuals and speeches, as well as proofreading technical papers, charts, summary sheets, project site visit reports, letters and other forms of documents originating within the Division. Services of the Section have been extended throughout NIH, PHS and DHEW to include institutes, divisions, the Surgeon General's Office and the Secretary's Office.

Mail and Files Section - This Section receives and processes for delivery a large volume of mail coming into the Division each day, and maintains audit files for the nine institutes, the Bureau of State Services, Division of Research Facilities and Resources, as well as for DRG. Over 22,000 applications for research grants were received during 1963 and early 1964. A total of 1,062 were received one particular day during the March 1964 deadline period, the highest number on record for any previous day. Also received and distributed during this period were 16,000 reprints (publications resulting from PHS grant supported research); over 2,300 progress reports (a detailed report to accompany competing continuation applications) in 40 copies each; and over 1,600 pieces of certified or registered mail. Maintenance of official correspondence files for the Division, as well as current correspondence for the Office of the Chief, is another function of the Section.

Travel Section - This Section's function is to receive and process for payment travel vouchers from Division personnel, review panels, committees, and study section consultants performing in an official capacity for the Division or in the various review processes for which the Division is responsible. During 1963, over 10,000 travel vouchers were received and processed involving an expenditure of close to $2½ million. In addition, this Section offers assistance to Division travelers in plotting itineraries, obtaining tickets, travel advances, or assistance in voucher preparation.

DIVISION OF RESEARCH SERVICES

Report of Program Activities
January 1, 1963 through June 30, 1964

A. Objectives

The paramount objective of the Division is to provide a wide variety of scientific, technical, and engineering services to support and further the research programs of the National Institutes of Health. Since virtually all of these services are affected by changes in scope and direction of the Institute programs, the Division makes a continuing effort to keep informed of Institute plans and adjusts its organization, staffing, and functions accordingly.

B. Current Programs

The Division of Research Services, which employs approximately 1,300 persons with almost 200 individual occupational skills, is composed of an Office of the Chief and eight branches: Computation and Data Processing, Environmental Services, Instrument Engineering and Development, Laboratory Aids, Library, Medical Arts and Photography, Plant Engineering, and Research Facilities Planning.

The programs of the Division can be divided into two broad classifications:

(1) Programs in direct support of research

a. Development, design, and fabrication of special-purpose instruments.
b. Production of bacterial and tissue culture media.
c. Preparation of sterile glassware.
d. Production of genetically controlled small research animals.
e. Quarantine and conditioning of larger research animals.
f. Animal surgery and recovery.
g. Animal disease control.
h. Photographic services of all types.
i. Medical arts services, including medical illustration and model making.
j. Development, testing, or control of special environments needed for research or clinical purposes.
k. Computation and data processing services in support of individual biomedical research projects.
l. Library services.
m. Foreign language translation.

(2) Programs related to NIH facilities and general environment

a. Engineering liaison in the design and construction of new NIH facilities.

b. Engineering work directed toward the development of improved facilities and equipment for biomedical research.
c. Engineering and craft services required for the alteration and maintenance of the NIH plant and facilities.
d. Maintenance of the NIH grounds.
e. Environmental services designed to maintain, protect, and improve the health and well-being of NIH patients and employees and of laboratory animals used in NIH research programs.

C. Accomplishments

Construction of New Facilities

The Division provides engineering liaison in the design and construction of new NIH facilities. Two major construction projects were started during the past 18 months. In March 1964, a four-story extension to Building 12 was started. This extension will house offices and service-connected laboratories, many of which are now located in the Clinical Center. The first phase of construction at the NIH Animal Center was begun in 1963. This will include a farm animal building and a kennel building for the holding and quarantine of animals for research.

Significant renovation projects include conversion of the top floor of Building 12 to provide more space for the central computation and data processing facility and remodeling of space in Building 10 to provide an intensive patient care unit for cancer surgery.

The most effort during this time was spent on the design aspects of forthcoming major construction projects. Engineers related to the design program of the Division have been engaged on more than 15 major projects totaling $67,843,000 in design and construction costs. These include new buildings such as the Cancer and Neurology-Mental Health Buildings as well as major additions such as the DBS Extension and the General Office Building Extension.

Division effort in regard to the construction program also includes engineering work directed toward the development of improved facilities. For example, in laboratories where any toxic or noxious fumes are generated, good fume hood performance is essential. Heretofore, the only fume hood which could be expected to give first-rate performance was designed on the basis of having sufficient room air available to provide the necessary velocity through the face of the hood. This is very expensive since all room air must be heated or cooled. Division engineers developed a fume hood for the new NCI and NIMH/NINDB Buildings which will perform satisfactorily when using 70 percent outside air and only 30 percent room air.

Also, because laboratory animal care facilities are vitally important to NIH, a research and development project promoting improvements in animal care facilities has been undertaken. This project includes assistance in the preparation of the Program of Requirements for the small-animal production facilities for new NIH projects, mechanization of animal care processes,

especially in the areas of cleaning and watering, and new designs for cages for the NIH Animal Center, incorporating the principles of mechanization and improved fabrication techniques.

Building 10-A (Surgical Wing)

The new Surgical Wing, more than any one project, demonstrates the extent of the Division efforts to provide adequate facilities and research environment. Construction of the Surgical Wing (Building 10-A) of the Clinical Center was completed and the wing occupied during 1963. All items of environmental health significance in Building 10-A were checked before it was placed in operation. This included a detailed sanitary survey of the whole building, adjustment of the ventilation systems in the operating suites, measurement of the number of bacteria in the air entering the operating suites, and determination of the vibration levels in all parts of the structure.

While the highly satisfactory performance of the air supply system in the operating suites of Building 10-A cannot be attributed to much that was accomplished in this reporting period, or even by staff members currently assigned to the Division, the fact remains that the functional design was largely the effort of the Environmental Services Branch. Bacterial counts in the air of the new operating suites are about one-quarter of those to be expected in a conventional operating suite. Division sanitarians are now a common sight as they perform periodic bacteriological surveys of the Surgical Wing as well as other operating rooms in the Clinical Center.

The instrumentation system installed in the Surgical Wing was mainly the responsibility of a DRS engineer. He consulted and cooperated with surgeons, anesthesiologists, hospital nursing staff, the building architect, engineering firms, and commercial instrumentation firms to help produce one of the most advanced systems in this country for monitoring physiological data of patients in surgery.

Computation

Of major significance during the reporting period was the acquisition of a second Minneapolis-Honeywell 800 computer, which doubled the computing capacity of the Computation and Data Processing Branch. The second computer, as the first, has been manned on a three-shift basis, with additional weekend operation when necessary.

An IBM 1620 computer was also acquired for use in a training program designed to provide laboratory scientists with the opportunity to explore fully the relationship of their scientific problems to the computer, and to assist them in solving some of their problems. The response to the program has been excellent, and it has helped to bridge the gap between laboratory scientists and the computer sciences.

In response to a growing need for the rapid and versatile conversion of laboratory data from analog to digital form and for closer interrelation between some investigators and the computer, detailed specifications for a hybrid

computing system were developed by NIH and have been approved by the Office of the Surgeon General and the Office of the Secretary. The system, which will be operated on a partnership basis with the Laboratory of Clinical Biophysics, NHI, will combine computational and analog-to-digital capabilities.

Phase I of the NIH Computer Configuration Study was completed in cooperation with a team from the National Bureau of Standards. The Study has as its objective the establishment of basic and long-term equipment needs of the central computer facility at NIH.

The Division has furnished key personnel to the group working toward the establishment of a new Division of Computer Research and Technology.

Instrumentation Support

As the requests for service for instrument engineering, fabrication, and maintenance continue to increase, the utilization of contracts with outside firms increases commensurately. In keeping with this program, the Division engineers and supervisors have become thoroughly acquainted with the capabilities of outside firms as well as becoming familiar with the ways of handling and monitoring outside contracts for engineering and development and for the design, fabrication, and maintenance of instrumentation.

One of the major developments expected for the near future is increasing interest and participation of commercial consultants and manufacturers in medical instrumentation. This will provide a growing supply of available engineering and instrumentation support. The program plans of the Division are directed toward tapping these commercial resource facilities and making them available to NIH scientists and surgeons.

The experimental and clinical nature of intramural research at NIH, and its continued growth, have created an increasing demand for preventive maintenance, timely on-site diagnosis and repair, and operations work on biomedical instrumentation systems at NIH. To meet this need, a new section was activated the beginning of F.Y. 1964 and staffed with personnel possessing special training to provide the high-level skills and abilities needed to perform this work.

As part of the effort to provide more efficient emergency service, the facilities and capabilities of the Building 10 satellite instrument shop were expanded by the addition of new personnel, including a glassblower. This unit, although still understaffed, offers Clinical Center researchers and investigators quicker service on both routine and emergency jobs by eliminating the time lag previously required when sending instruments to or requesting service from the parent facility located in Building 13. In addition, plans are currently being prepared for the relocation of this unit within the Clinical Center, with resultant additional working space and still better service to the researchers. The move to this new space should be accomplished within F.Y. 1965.

Shop Services and Maintenance

During the period January 1963 to June 1964, the Division, for the first time in its history, succeeded in continuously staying abreast of craft shop service demands. This was accomplished in spite of the fact that demands for service were at an all-time high. This improvement in service was achieved by improvements in planning, scheduling, and methods of procuring materials, as well as by the judicious use of private contractors. This has resulted in a more responsive service to NIH staff and a more economical use of people and facilities than had been achieved in previous years.

The plant operation and maintenance workload has increased since January 1963 due to the opening of Building 10-A and the animal quarantine building at the NIH Animal Center. As part of a continuing search to reduce costs and increase the effectiveness of these services, a pilot equipment monitoring system was installed in Building 7 for continuously monitoring the temperatures of cold rooms, hot rooms, and deep freezers. The manpower savings alone have been sufficient to give consideration to employing the system on a broader scale.

Library Services

As part of a program to use more effectively the limited space for the Library, considerable attention was directed to improving the content of the collection and the physical arrangement of the Library during the past 18 months. An intensive weeding program to provide space for new volumes and remove little-used obsolete materials was undertaken. Procedures were instituted to provide better security for the Library collection.

In an effort to make the journal collection more accessible, a crash program directed at eliminating the backlog in binding was instituted. Approximately 10,000 volumes in excess of the number normally bound were handled. The Library's capability for providing photocopies of journal articles was also increased. The photocopy service effectively increases the availability of journals.

Emphasis was placed in filling vacancies that occurred in the Library with well-qualified reference librarians with some scientific background.

Variety of Visual Communications Services Increases

Although the bulk of the Division's requests for photography and art services are for charts, graphs, and standard photographs for publication purposes, there has been a significant increase in other forms of visual communication services.

Photography personnel have worked with investigators in an increasing demand to record a wide variety of clinical and laboratory studies such as the action of cat vocal cords, the repair of atrial septal defects, and chromatographic analyses.

Medical illustrators are compiling an important medical record in a collection of ophthalmological illustrations of young children with neurologic difficulties. There is no previous record of such paintings having been done.

A detailed and extensive set of colored slides illustrating draping techniques for 12 distinct surgical procedures was processed for the Clinical Center for teaching purposes.

Also, exhibits have become a much more popular form of communications. In the past 18 months, 33 exhibits were designed and over 200 shipped to a variety of scientific meetings.

NIH Animal Center

Progress has been generally satisfactory on the first phase of construction of the NIHAC facilities. All of the dog quarantine operation was transferred from Bethesda to temporary quarantine buildings at the Center, pending completion of the permanent quarters late in 1964.

Germfree Animals

The germfree animal rearing program developed from a pilot operation to a small production facility during 1964. The staff has been extremely successful in this program and has raised production to an average of 450-500 germfree animals per month. An arrangement has been worked out for placing a plastic isolator with animals in the scientist's laboratory for his use and subsequent return.

Animal Quality Improved

New techniques involving improved barrier systems, separate cage washers, and increased bacteriologic monitoring have led to increased productivity and higher quality in mice. Improved inspection systems and more rigid requirements of dog and cat suppliers, as well as an increase in quarantine period, have permitted the issuance of higher quality animals to the investigator.

Other improvements in animal quality have been achieved by more effective disease control. Recent improvements in monitoring techniques permitted the early detection and elimination of coccidiosis, a highly infectious protozoan disease, from two rabbit colony rooms.

The causative agent of the most commonly occurring pneumonia of guinea pigs was found to be Bordetella bronchiseptica. A vaccine was prepared and found to be effective in controlling this disease in the Strain 13 guinea pig colony. Since last year this colony, a valuable inbred strain, has been restored to normal status following studies which revealed dietary deficiencies.

Staffing Changes

There were several staffing changes made in this reporting period designed to strengthen the Division's ability to respond to the needs of the NIH program.

Two Associate Chiefs were assigned to the Office of the Chief. The Associate Chief for Engineering Resources is responsible for the development and coordination of the programs of the Plant Engineering Branch, Research Facilities Planning Branch, Instrument Engineering and Development Branch, and Environmental Services Branch. The Associate Chief for Laboratory Resources is

responsible for the development and coordination of the programs of the Laboratory Aids Branch, Library Branch, and Medical Arts and Photography Branch. In addition, he serves as Scientific Director for the Division.

An Assistant Chief was named Associate Chief for Computer Resources. Besides being responsible for the program of the Computation and Data Processing Branch, he has devoted a major portion of his time to planning the organization of the new Division of Computer Research and Technology.

A Chief of the Library Branch was recruited, thereby relieving one individual of the responsibility for both the Library and Medical Arts and Photography. This has permitted a more effective development of both of these Branches.

D. Problems

Personnel

The imposition of personnel ceilings on the number of people employed in sections financed by the Service and Supply (Revolving) Fund greatly reduces the effectiveness of performing services requested by NIH users of the Division facilities. This has been met to some degree by use of outside contractors; however, there are insufficient commercial resources to meet the total backlog. Consequently, overtime work by regular employees is used to combat the problem with limited success.

With the imposition of a ceiling on Revolving Fund positions, there were some instances where no new positions were filled for 9 months. In the case of the Computation and Data Processing Branch, the situation has now been relieved with an increased allowance. However, the Branch now faces the formidable task of simultaneously training many new employees.

The Computation and Data Processing Branch continues to lose experienced mathematicians and technical personnel to private industry. Although recruiting efforts are directed toward experienced personnel, the Branch usually must resort to hiring young, inexperienced individuals just out of college. After these young people are trained in programming and gain experience, they become vulnerable to the lure of higher salaries being paid by private industry.

In view of the problem of recruiting well-rounded trade craftsmen, the Plant Engineering Branch has developed an extensive training program using in-service (NIH-PHS) training, other government training facilities, and non-government training programs. Also, plans are being made, in conjunction with the Department of Labor, to develop an apprenticeship program for certain of the maintenance crafts.

Construction

NIH is continually confronted with loss of time in obtaining approvals and clearances during the different stages of design. Invariably, it has been our experience that the review periods are considerably longer than provided for in the A/E contract. Part of the problem is that the review periods

agreed upon between the Government and the A/E are unrealistically short. Another problem is the lack of sufficient personnel at PBS in certain disciplines to perform the review.

Efforts have been made to accelerate the review periods at NIH and at the PBS level. RFPB Project Engineers are now required to maintain close supervision of the design schedules which are a part of the A/E contract. In March 1964, the PBS recognized that its backlog of design reviews was increasing and issued instructions to its personnel which would accelerate review processes. It is not known whether this accelerated effort will be for a limited time only, or will be the continuous policy of PBS.

One other continuing corrective measure which NIH pursues is that in which the Chief, DRS, periodically reviews the NIH program with the Assistant Commissioner for Design and Construction, PBS. These contacts have been fruitful in specific instances. However, it appears that there is limited authority for decision at the PBS working level.

The PBS, which has direct responsibility for construction contract administration, has encountered increasing difficulty in hiring and retaining competent personnel for construction supervision and inspection. In an effort to overcome this lack of personnel, our most recent contracts with A/E firms have included provisions for supervision of the construction by the A/E, at the option of the Government.

TABLE OF DRS PROJECTS
January 1, 1963 through June 30, 1964

Laboratory Aids Branch

Serial Number	Title
4.1	Effect of Hydrochloric Acid and Chlorine Treatment Upon Pseudomonas Aeruginosa and Coliform Bacteria in Mouse Drinking Water
4.2	A Comparison of Two Diets for Mouse Production
4.3	Cooperative LAB-ESB Study of Pseudomonas Aeruginosa in Animal Water Bottles
4.4	Establishing and Producing Germfree Hamsters
4.5	Breeding of the Stump-Tailed Macaque Monkey (Macaca Speciosa) in Captivity
4.6	The Generation Time of Mast Cells of the Rat
4.7	Acute Epizootic Pneumonia in the Guinea Pig Colony
4.8	Chronic Murine Pneumonia of the Albino Rat
4.9	Mucoid Enteritis of Rabbits
4.10	Study of Causes of Death in Strain 13 and Strain 2 Inbred Guinea Pig Colonies
4.11	A Survey of Mycotic Diseases in Domestic Animals Submitted by the Communicable Disease Center, Kansas City, Kansas
4.12	Estimation of Allantoin in Body Fluids of Animals
4.13	Induction of Reticulocyte Response in Goats
4.14	Investigation of a Means for Clinical Diagnosis of Chronic Respiratory Disease of Rats
4.15	Pathology of Dirofilaria Immitis Infection of Known Inoculation Date and Dose in Dogs
4.16	Trial of Parlett Gel Diffusion Test for Tuberculosis in Rhesus Monkeys

Laboratory Aids Branch (continued)

Serial Number	Title
4.17	Focal Necrosis of the Liver of Rabbits
4.18	Measles (Rubeola) in Rhesus Monkeys
4.19	Evaluation of Shigella Flexneri (Serotype 4) Attenuated Vaccine
4.20	Evaluation of Programs for Immunization of Quarantine Dogs: Pilot Study
4.21	Effect of Various Day-Lengths on the Productivity of Mice

Instrument Engineering and Development Branch

Serial Number	Title
8.1	Conversion of Gradient Elution Control System to Punched Tape
8.2	Instrumentation System for Cardiac Surgery
8.3	Patient Monitor for Cardiac Recovery Room
8.4	Nucleic Acid Analyzer
8.5	Microelectrode Preamplifier

June 1964

January 1, 1963
through June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-2
Serial Number

2. PLANT ENGINEERING BRANCH

3. R. R. Holliday
Branch Chief

I. SUMMARY

During the period January 1963 to June 1964 the Plant Engineering Branch, for the first time in history, succeeded in continuously staying abreast of service demands. This was accomplished in spite of the fact that demands for service were at an all-time high. This improvement in service was achieved by improvements in planning, scheduling, and methods of procuring materials, as well as by the judicious use of private contractors. This has resulted in a more responsive service to NIH staff and a more economical use of people and facilities than had been achieved in previous years.

Also during this period, the operation of three decentralized area maintenance units has been perfected so as to provide immediate service for minor troubles such as clogged plumbing, light bulb replacements, air conditioning problems, and utility leaks. During the period since January 1963, telephone orders for this service have been received at an average rate of 75,000 per year.

Although the professional engineering staff of the Branch has to plan only slightly more than one percent of the 18,000 written orders for work each year, most of these are sizeable construction projects. They prepare plans for large station labor jobs and for jobs performed by contract. They also direct and review the work of professional services contractors engaged for performing engineering services.

In this reporting period some of the more important projects include conversion of the top floor of Building 12 to provide more space for the central computation and data processing facility and renovation of space in Building 10 to provide an Intensive Patient Care Unit for cancer surgery. Also supervision of the design of the extension to Building 12 was completed and the contractor has started work on this four-story facility that will house offices and service-connected laboratories, many of which are now in the Clinical Center.

The plant operation and maintenance workload has increased since January 1963 due to the opening of Building 10-A and the animal quarantine building at the NIH Animal Center. As part of a continuing search to reduce costs and

increase the effectiveness of these services, a pilot equipment monitoring system was installed in Building 7 for continuously monitoring the temperature of cold rooms, hot rooms, and deep freezers. The manpower savings alone have been sufficient to give consideration to employing the system on a broader scale.

In view of the problem of recruiting well-rounded trade craftsmen, the Branch has developed an extensive training program using in-service (NIH-PHS) training, other government training facilities, and non-government training programs. Also, plans are being developed, in conjunction with the Department of Labor, to develop an apprenticeship program for certain of the maintenance crafts.

II. BRANCH PROGRAMS

A. Objectives

The mission of the Plant Engineering Branch is to provide responsive support to the medical research mission of the National Institutes of Health by furnishing as expeditiously and as economically as possible the services described below:

Operation and Maintenance: These services consist of operating, maintaining, and repairing NIH physical, mechanical, electrical, architectural, and landscaping facilities as well as maintaining and repairing laboratory and research apparatus.

Engineering: These services consist of developing and preparing plans and specifications for alterations, repairs, and extensions to the existing facilities, administering and inspecting construction work performed by private contractors, and providing professional engineering services as required.

Construction: These services consist of altering, installing, and fabricating facilities and equipment for research programs. In this capacity the Branch furnishes mechanical, electrical, and architectural craft services.

B. Program Progress and Accomplishments

Construction By Station Shops: During the period January 1963 to June 1964 the Plant Engineering Branch, for the first time in history, succeeded in continuously staying abreast of service demands. This was accomplished in spite of the fact that demands for service were at an all-time high.

That service demands were high can be realized by observing Chart No. I which reports the total dollar value of material issued per quarter since July 1960. Note the rapid growth to about June 1963 and the leveling of the growth since that period as reflected by this growth indicator.

That more responsive service was provided on a continuing basis can be observed by comparing Chart No. II with Chart No. III. These two charts show the average shop work backlog in the Branch from February 1961 to the present time. The backlog of work at any period in time is a good indicator

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERING BRANCH

MATERIAL SUMMARY

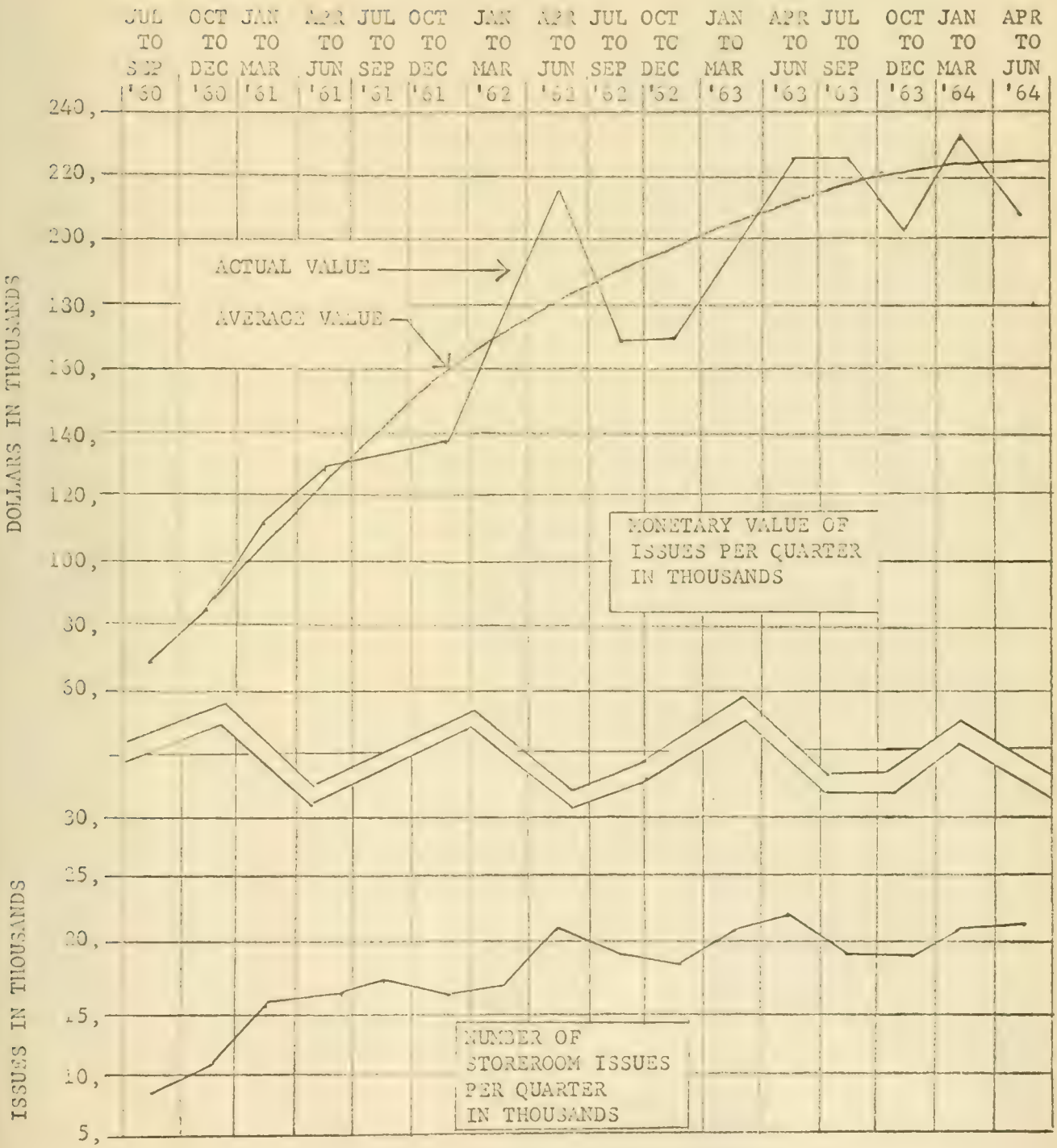
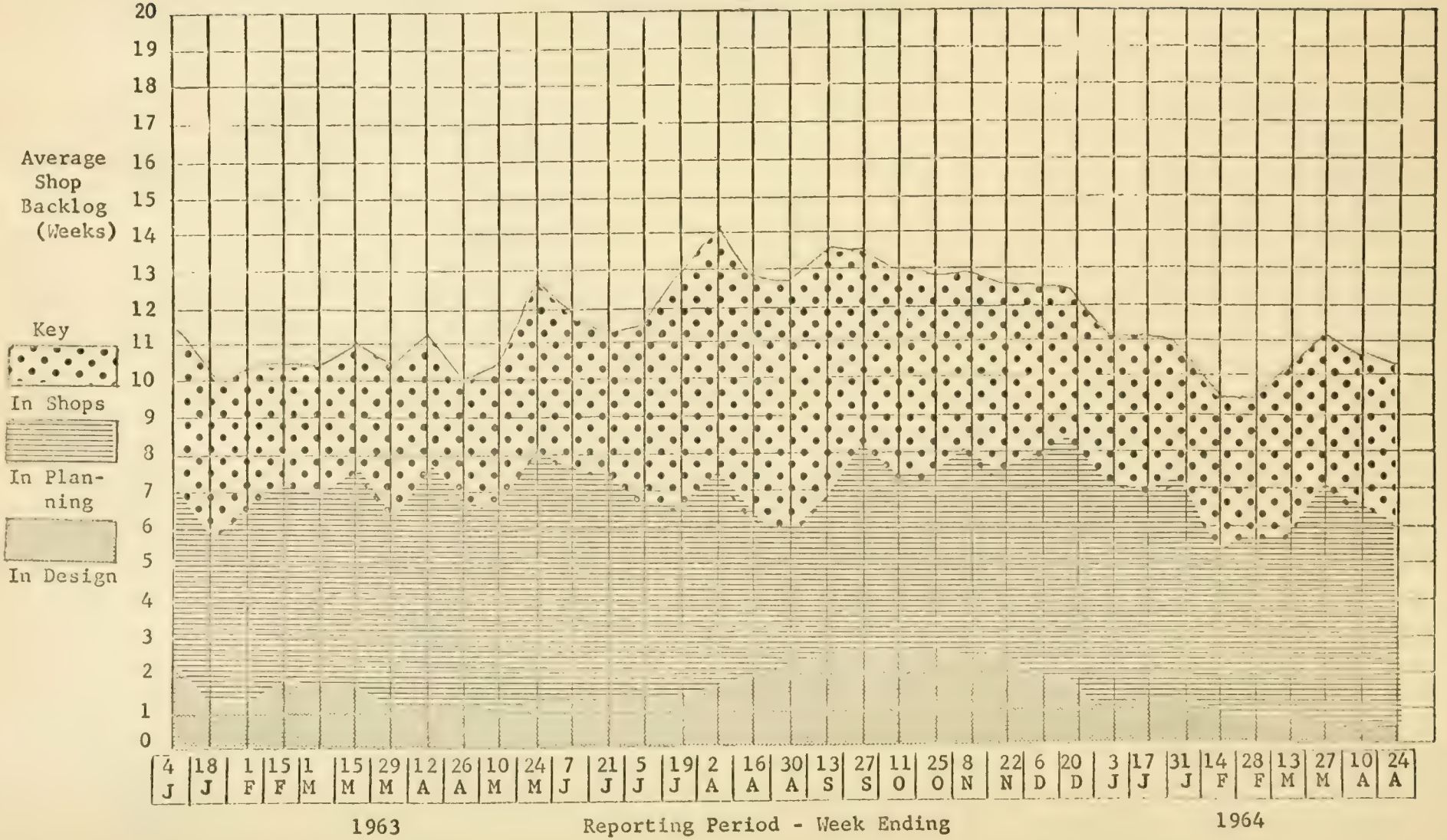


Chart No. I

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERING BRANCH

SHOP WORK BACKLOG SUMMARY

Reporting Period January 1963 thru April 1964



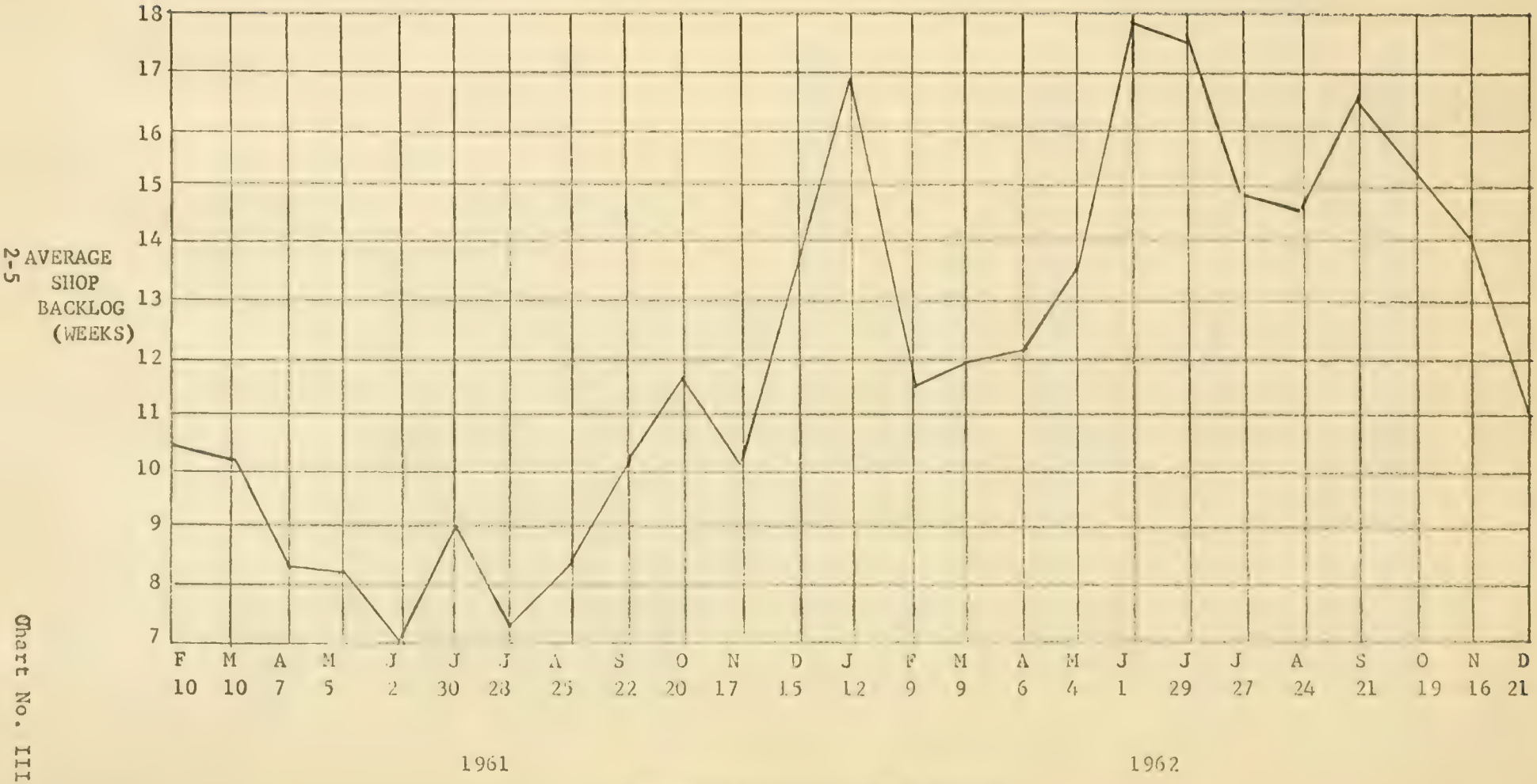
2-4

Chart No. II

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERING BRANCH

SHOP WORK BACKLOG SUMMARY

Reporting Period February 1961 thru December 1962



2-5

Chart No. III

NATIONAL INSTITUTES OF HEALTH
DIVISION OF RESEARCH SERVICES - PLANT ENGINEERINB BRANCH

MATERIAL/LABOR RATIO SUMMARY

($ of materials used per labor manhour expended)

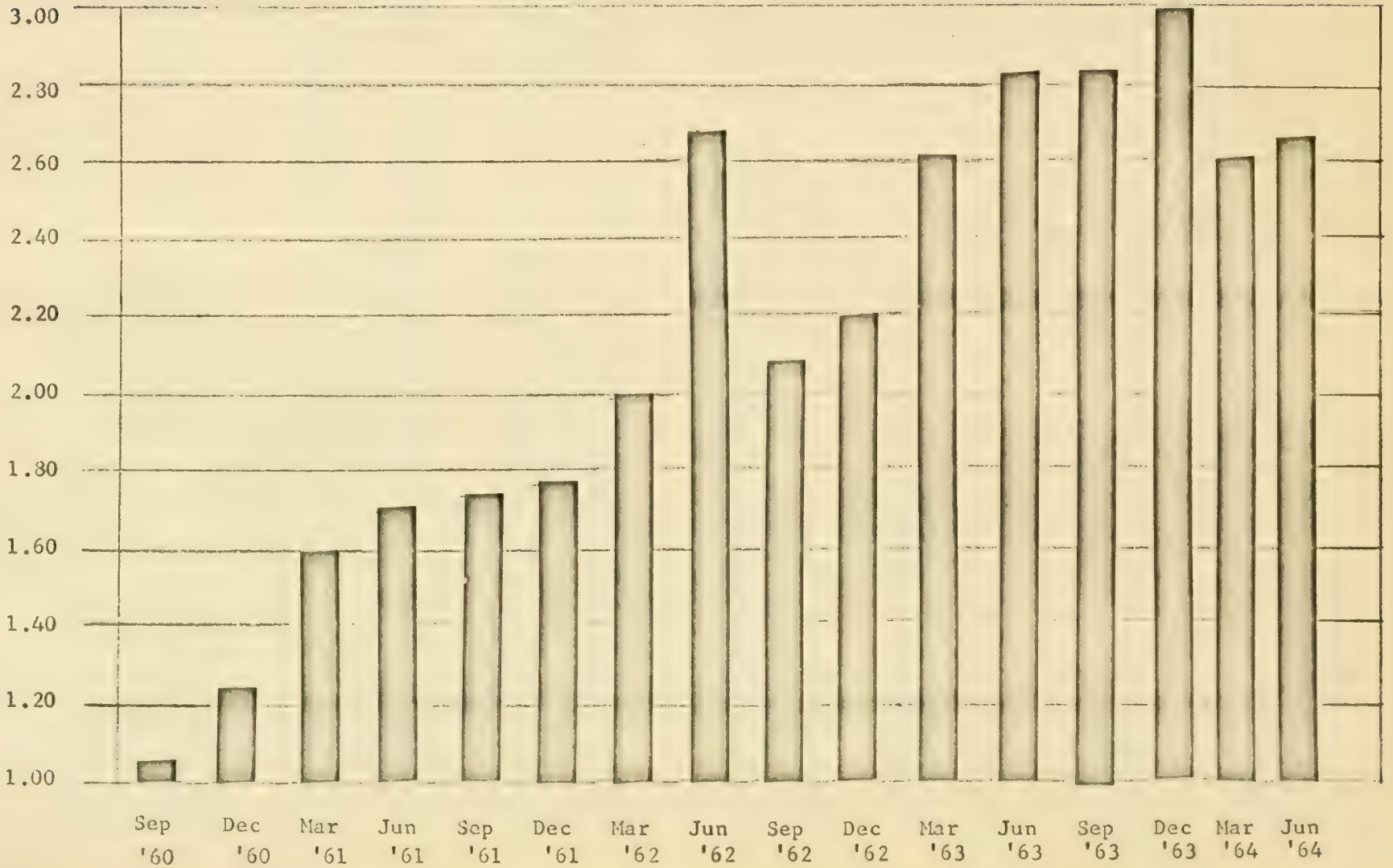


Chart No. IV

of the time required to process a job from inception to completion, since it is a measure of the time a job may lie idle awaiting available manpower to do the work. From experience it has been found that a backlog of about eight (8) weeks is optimum; it provides adequate load to keep manpower gainfully occupied while at the same time necessitating a minimum of queing at the various stages of job processing.

Note, from Chart No. II, that while the backlog goal of eight (8) weeks was never achieved, the load was maintained much more uniformly and exceeded twelve (12) weeks for only a short period compared to the previous two-year period reported by Chart No. III.

This improvement in service was achieved by: (a) improvements in planning and estimating techniques and skills; (b) a reduction in material procurement time through the application of short form procurement methods and increased emphasis to procurement follow-up; (c) the use of refinements in job scheduling, including the application of the Critical Path Method technique; and (d) the judicious use of private contractors.

That this improvement in responsiveness of service was not accomplished at the expense of efficiency is indicated by Chart No. IV, which compares the relationship between material costs and manhours of labor expended since September 1960. The dramatic improvements in labor efficiency did not continue after March 1963 as compared to previous years, but a continued high level of performance was maintained as reflected by the material/labor ratio indicator.

Requests for service are received by the Branch in the form of written work orders and by telephone. Telephone requests are received by three decentralized area maintenance units for minor services such as clogged plumbing, light bulb replacements, air conditioning problems, and utility leaks. All other requests are received in the form of written work orders by one central work reception unit.

During the period since January 1963, telephone orders have been received at an average rate of 75,000 per year and written orders at an average rate of 18,000 per year. Little or no formal planning is needed for the telephone orders. Only slightly over one percent of the 18,000 written orders are planned by the professional engineering staff of the Branch. The remaining 99 percent are planned and estimated by craft technicians. About 60 percent of the jobs planned by the professional engineering staff are performed by private contract.

Construction By Private Contract: Most large jobs (400 manhours or more) and jobs requiring special skills not employed by the Branch are performed by private contractors.

During fiscal year 1963, 255 projects having a total cost of $2,343,000 were completed by private contractors. During the first ten months of fiscal year 1964, 241 projects having a total cost of $1,103,000 were completed by private contractors.

Work in progress, being performed by contract, at any point in time since January 1963 had a total dollar volume of from 2.5 to 3 million dollars.

Engineering Services: During the 18-month period beginning January 1963, the professional engineering staff of the Branch prepared plans for large station labor jobs and plans and specifications for jobs performed by contract, directed the design efforts of professional services contractors engaged by the Branch for engineering services, and reviewed the work of professional services contractors engaged by others for the design of new NIH facilities.

A summary of work completed during the period follows:

Type	Quantity Completed	Actual or Estimated Construction Cost
Professional services contracts	18	$1,993,000
Staff design projects for contract work	103	2,062,000
Staff design projects for shop work	101	161,000
Engineering studies or surveys	26	---
Total		$4,216,000

A few of the more important of these projects are listed below.

Alterations

1. Conversion of the top floor, Building 12, to office space from animal space for the Computation and Data Processing Branch, DRS - $281,000.

2. Renovation of the south wing, 2nd floor, Building 1, for DRS offices - $35,000.

3. Renovation of space adjacent to the operating facilities, 10th floor, Building 10, to provide an Intensive Patient Care Unit for cancer surgery patients - $60,000.

Maintenance, Repairs and Improvements

1. Repair of elevators for Buildings 5 and 6	$75,000
2. Install revolving doors at main and west entrances to Building 10	20,000
3. Widening of Center Drive and South Drive	250,000
4. Resurfacing of roofs, various buildings	16,500
5. Improvements to high voltage distribution system	30,000

New Building Construction

1. Extension to Building 12; a four-story addition containing 62,500 gross square feet for offices and light laboratory functions - $1,350,000.

2. Animal Quarantine Building #2; a temporary single-story structure for dogs erected at the NIH Animal Center - $182,000.

Surveys or Studies

1. Anaerobic chamber for Building 3; a research study was undertaken to determine the feasibility and practicality of developing such an environmental chamber for the use of the National Heart Institute. A decision has been made to proceed with this project based on favorable study results.

2. Building 31 solar load problem; a study was undertaken to determine what, if any, practical modifications could be made to the mechanical systems and/or architectural exterior features of this structure to reduce the overheating problem experienced in winter months due to high heat gain from the sun. The determination was that no practical measures are available to overcome the system deficiencies, but refinements in operational procedures can reduce the problem.

3. Supply air deficiency, Building 10; a study was made to determine the magnitude of the problem and to develop a concept and cost evaluation for overcoming it. Conclusions developed were the basis for budgeting to correct the deficiency.

Operation and Maintenance Services: The plant operation and maintenance workload increased since January 1963 by the opening of Buildings 10-A and an animal quarantine building at the NIH Animal Center. These buildings represent an increase in gross floor space of about 55,000 square feet.

Approximately 100 employees are currently engaged in routine operator inspection and operator maintenance functions associated with the operation and maintenance of buildings, utilities, and research equipment at the NIH Reservation and Animal Center.

As part of a continuing search to reduce these manpower costs, a pilot equipment monitoring system was installed in Building 7 for continuously monitoring the temperatures of cold rooms, hot rooms, and deep freezers. This pilot system has resulted in a manpower savings of approximately 37/100th of a man-year, or $2,500 per year. The system cost was $16,200, hence the cost can be amortized in less than seven years from labor savings. Considerations are now being given to employing the system on a broader scale.

Grounds: Drought conditions prior to and during calendar year 1963 resulted in the lowest water tables in many years. Large trees have suffered most from the drought. Several large oaks near Building 15-K and along South Drive will be lost. The maples along North Drive are in danger of being lost. Wetting agents, mulches, and anti-dessicating foliar coatings have been used to aid in the application and conservation of moisture. Deep feeding of trees has also been employed with success.

Permanent lawn irrigation systems were installed in the lawn areas in front of Building 1 and Building 10. Plans include employing similar systems in other key locations in the interest of maintaining better lawns.

Personnel: As of April 24, 1964, the Branch employed 536 permanent employees and 9 temporary employees for a total of 545, which is 7 employees fewer than the 552 on board as of January 1, 1963. Although the use of

temporary employees has given the Branch access to an additional source of labor, there has been ever-increasing difficulty in recruiting and retaining skilled craftsmen, especially Fixed Industrial Equipment Operators.

Training: The Branch supported approximately 610 man-days of formal classroom training, slightly more than an average of one man-day per employee. Of this total 350 man-days were provided within the Branch itself, and an additional 108 man-days consisted of in-service (NIH-PHS) training. The balance was made up of 14 days training provided by other governmental facilities, and 138 man-days of training in non-governmental institutions. The North and South Buildings Units, the Clinical Center Unit, and the Elevator Unit continued formal plans of instruction in maintenance and operation of plant equipment. In addition, the Chief, Shops Section, has conducted three courses on Program Evaluation and Review Techniques (PERT) for approximately 30 Shop Foremen and Planner-Estimators.

Difficulties experienced in recruiting and retaining the types of highly skilled craftsmen required for prompt, economical maintenance of a complex research plant, as well as recognition of the need for upgrading the quality of the maintenance force, have resulted in much consideration of an apprenticeship training program. As a result, information concerning apprenticeship programs in general has been obtained from the Naval Ordnance Laboratory, White Oak, and from the Bureau of Apprenticeship Training of the U. S. Department of Labor. Tentative steps are being taken to draft proposed four-year apprenticeship programs for certain of the maintenance crafts. It is anticipated by the Plant Engineering Branch and by a spokesman of the Bureau of Apprenticeship Training that the problem of recruiting well-rounded trade craftsmen will become acute within the next five years.

Awards: The awards program has continued to flourish as suggestions for various improvements are being submitted at the rate of two per week. Thirtee awards were made for suggestions and/or work performance. It is clear that the program has "caught on", and it is reasonable to expect that further growt of the program and its concomitant benefits will ensue.

C. Program Plans

Long and short range plans used to direct the day-to-day business of the Branch include the following: (a) operating budget and related reports; (b) preventive maintenance system from which is generated an inventory of major repair and improvement projects and related data for budgeting, plus immediate needs for general maintenance and repair; (c) weekly workload reports which reflect the estimated craft labor requirements by trade; (d) monthly workload reports which reflect the estimated engineering manpower requirements for engineering services by discipline; and (e) weekly personnel status reports which report the available manpower by organizational unit resulting from personnel attrition and recruitment.

In addition, program improvements planned for the coming year include: (a) strengthening the professional engineering design staff to provide the capability needed to process an increase in work resulting from major repair and improvement projects and new building construction; (b) the establish-

ment of a competency within the Office of the Chief for the purpose of emphasizing continuous review and analysis of operating procedures; (c) the establishment of procedures for improving the utilization and control of personal property (hand tools, portable equipment, etc., and a tool crib with simple procedures for issuing, repairing, retrieving, and controlling property; and (d) a complete review of current personnel management practices in the wage board areas for the purpose of establishing standard principles applicable to position classification, job assignments, and general work rules.

June, 1964 January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-3
Serial Number

2. MEDICAL ARTS AND PHOTOGRAPHY BRANCH
Branch

3. Malcolm S. Ferguson
Branch Chief

I. SUMMARY

Emphasis over the past 2 years on coordination of activities of the Sections and Branch Office has resulted in the increased efficiency of Branch operations. Training of personnel received special support in order to raise and maintain the quality of performance and to keep the staff abreast of the latest techniques for providing modern and efficient art and photographic services to NIH scientists.

Major contributions in the photographic services include the introduction of high-speed photography as an aid to investigators in the analysis of rapid movement, the acquisition of automatic equipment for negative film processing and certain aspects of printing, improved photomicrographic services, and improved methods of producing projection slides. Art personnel have been able to accomplish a greatly increased volume of clinical and graphic illustration with little additional staffing because of refinement of techniques, acquisition of modern equipment, and adaptation of new methods. There has been a marked increase in art for slide production, an expansion of the exhibits program and continuing stress on ophthalmological illustration.

The Branch has been recognized as a focal point at NIH for training in visual communications, several trainees from other institutions having spent periods of time in the Branch. These trainees have introduced new ideas and have often contributed to ongoing support services during their training period.

II. BRANCH PROGRAMS

A. Objectives

The Branch objectives are to provide documentary visual recording of biological phenomena and observations resulting from the research programs of NIH, to facilitate the dissemination visually of new scientific information to professional groups both here and abroad, and to apply visual media for the public understanding of biomedical knowledge.

B. Current Programs

The programs of the Branch include a wide range of art and photographic

services such as clinical illustration, general illustration, exhibits designing, statistical drafting, plastics fabrication, moulage making, publications design, clinical and laboratory photography in both black and white and color, public relations and informational photography, photomicrography, line copy and slide production, and motion picture and animation production. All services continued to expand in scope in order to meet the increasing demands of the NIH scientific staff. The Branch seeks to broaden and improve its programs in order to support the research effort at NIH in the most effective manner.

C. Program Progress and Accomplishments

1. Operational Improvements

On February 1, 1963, the Chief of MAPB was relieved of the additional responsibilities of the position as Acting Chief of the Library Branch, thus making it possible to devote full time and attention to MAPB. Special attention has been directed toward coordinating the activities of the Medical Arts and Photography Sections so that the special abilities of each Section may be most effectively utilized in support of NIH programs. Planning for the training of staff members has been centralized in the Branch Office to provide better coordination of this important activity.

A management study of the Branch was conducted with the assistance of a management analysis specialist. Thirty-eight recommendations were made and several of these put into effect, resulting in improved operating procedures.

Automatic processing in the photographic laboratory was introduced by the acquisition of a roll-head easel which permits exposure of multiple prints on a roll-paper transport. The time to handle routine line prints was cut approximately 50 percent.

Clinical photographic services have shown improvement in performance, especially in photomicrography, since the staff was increased and an in-service training program was instituted. The direct photography of stained sections on 2 x 2 slides has produced an efficient routine and permitted handling of more requests for this service.

The relatively small art staff and continuing increase in workload made it necessary for artists to rely more and more on new equipment and the refinement of techniques. It was sometimes necessary to bend the design to make it conform to the equipment in order to meet short deadlines. In general, competencies have been available for handling difficult problems of visual communication related to NIH research.

A study of the NIH exhibits program was initiated and a survey is underway with plans for setting up some mechanism for weeding out obsolete exhibits to prevent overloading of storage facilities.

Contracting of exhibits to be built by commercial firms has been expedited and obstacles eliminated by the new contracting method recently set up by the Procurement Section of SMB.

2. Accomplishments

The following projects are highlights of the photographic and medical art accomplishments during the past year and a half.

There has been a marked increase in chromatography recording, agar plate and starch gel photographic recording, photomicrography of blood cells, smears, and live tissue. Informational photography for brochures has been emphasized by several Institutes.

Several hundred color slides illustrating instrument draping techniques for 12 distinct surgical procedures were prepared for the surgical nursing staff of the Clinical Center to be used for teaching and demonstration purposes. In addition, photography was done for a training atlas depicting sterile tray preparation. As training receives greater emphasis at NIH, the Branch is called on to provide more and more photographic services to implement these programs.

The design and preparation of art work for slides has grown considerably and is now an important part of the art production program. There has also been a dramatic shift in copy preparation work away from publications material to copy for use in the production of slides.

Numerous publications were designed, for example: "Nursing Recruitment","A Guide for Nursing Home Administrators", "Heart Research News", "The New Surgical Wing of the Clinical Center", "A Comprehensive Psychiatric Center", "The President's New Mental Health Plan", and "Pathways of Research in Mental Retardation".

Medical Arts drafting personnel designed 30 charts for the Surgeon General's Advisory Committee on Smoking and Health, and these were modified later to render them suitable for rapid publication.

Motion picture photography of the research report type continues to increase, and the quality of the films is improving. One of the important advances was the introduction of high-speed motion picture photography. Coordination of all motion picture activities has received greater attention in recent months.

Motion picture films of significance completed since January 1963 include such subjects as: "Measurements of the State of the Blood", "Replacement of Mitral Valve With Starr-Edwards Ball Prosthesis", "Total Replacement of Aortic Valve With Mueller Prosthesis", "Heart Research News", "Speech Mechanisms", and "Microelectrophoresis". In addition, motion picture personnel worked with investigators in recording observations on various clinical and laboratory problems, e.g. the handling of patients undergoing special neurological examination, action of cat vocal cords, repair of atrial septal defects, participation of mental patients in drug study programs, and the testing of efficiency of air circulation systems using smoke.

An important medical record is being compiled in a growing collection of ophthalmological illustrations of children with neurological difficulties aged 6 months to 5 years. The collection has great clinical value because there is no previous record of fundus paintings having been done for this age bracket. A series of ophthalmological drawings of the fundus depicting subtle degrees of macula and peri-macula pigmentation were prepared for use during patient examination in order to describe more accurately pigment densities and pattern.

The art staff has also constructed a variety of models as aids to NIH research programs. For example, a life-size articulate wooden model of a monkey was constructed for use as an aid in designing equipment and setting up experiments for a study of head injury resulting from blows such as may be caused by accidents. Models of the spleen and liver were vacuum formed in clear plastic using sculptured plastilene models of these organs rendered by a clinical illustrator. These hollow plastic models were used for cancer x-ray studies.

A rapid means for revising and up-dating exhibits was developed through the use of a new magnetic paint which, together with magnetized plastic tape, permits the mounting of objects to exhibit panels. This method provides easy alteration, eliminates remaking of panels, and saves material expense and many manhours.

Thirty-three exhibits were designed and 210 exhibits shipped to meetings (3 overseas) during this reporting period. One exhibit presented various aspects of comprehensive mental patient therapy at St. Elizabeths Hospital. Another exhibit "Axial Transverse Encephalography" was selected over 50 other exhibits for the Most Popular Exhibit Award at the meeting of the American Roentgen Ray Society.

The newly equipped Branch Conference Room has provided several groups with audiovisual facilities. A variety of audiovisual tools as well as closed-circuit television were installed in the conference room. In addition, a permanent exhibit of Branch activities has also been set up there to depict the services available to the NIH staff.

Fine and applied arts services were used widely and effectively at NIH by various offices. In just one instance the consultation and planning services of the Branch's Fine and Applied Arts Specialist resulted in a saving of $1,000, the approximate fee of an outside interior decorator. Besides providing these services to NIH, consultation was also given and plans drawn up for the renovation and decorating of the offices of the Surgeon General, PHS, the Secretary, DHEW, and the Conference Room of the House Appropriations Subcommittee, the latter at the request of Representative John Fogarty.

Training

Training of staff personnel has been conducted through in-service instruction and visits to visual communications organizations in the Washington area. These visits give staff members an opportunity to study different techniques and equipment, with the view of improving VA/PA services. In addition,

personnel have received training through organized courses offered in and away from this area, specifically in motion picture production and editing, new still photographic techniques, fabrication of plastics materials, technical illustration, and animation production.

The Branch has also provided training opportunities for varying periods of time to selected individuals from other organizations, e.g. the practical demonstration of acrylic techniques to a Florida hospital technician, experience for the development of a medical art program to an audiovisual director from a Mexican medical school, and a 10-month internship in operation of a complete biomedical visual communications facility for a staff member of the School of Medicine, University of Puerto Rico.

Members of MAPB staff are currently training students at the Department of Art as Applied to Medicine, Johns Hopkins School of Medicine, in ophthalmological illustration and plastics techniques.

D. Problems

Responsibility for storage and shipment of exhibits has been assumed over the years by the Medical Arts staff. With the number of exhibits now existing and the marked increase in their production, this responsibility has become extremely burdensome. Resolution of this problem has been receiving serious attention, and currently a study of various aspects of the exhibits program is in progress.

In January 1964, two clinical illustrators left the Branch for attractive positions elsewhere. With the increasing number of excellent opportunities for individuals with training in medical illustration this situation can be expected to continue. The Branch is addressing itself to the question of how to attract and hold competent and versatile illustrators.

The Branch has to deal with strong pressures from NIH requestors, especially prior to the Federation, American Public Health Association, AAAS, and various categorical meetings. Efforts are being made to better coordinate such requests within the Branch and to have requests brought in sooner. However, it will be a forlorn hope to expect that such pressures will ever entirely disappear.

It is difficult from a workload standpoint to handle large photographic duplication requests for individual requisitioners. Moves being made toward automating photographic processing will alleviate this problem somewhat. As a means of control the contractual mechanism is being promoted wherever possible when a volume of prints is required. Additional controls within the Institutes and Divisions must also be formulated.

E. Program Plans

The following are program plans and activities that will receive special attention over the next year or two:

The automation, as far as presently possible, of photographic negative processing and printing and slide production to standardize these services and increase production in these photographic areas.

The acquisition and use of additional devices for production of certain types of art work so that the staff is better able to handle its workloads.

Development of a comprehensive animation program relating to both the graphic and medical art areas.

Exploitation of the potentials of high-speed photography in support of research at NIH. The provision of film analysis services to investigators who are using the motion picture camera as a research tool.

Emphasis on developments in the plastics field in support of NIH research programs and exhibits design and production.

Production of appropriate art and photographic materials for use in NIH training programs, e.g. training of housekeeping staff, animal caretakers, nurses, ward attendants, etc. Various media are to be used in experimental approaches to these training programs.

Initiation of a research and development program in the photographic area of the Branch, this to be centered around academically trained photoscience technologists. It is expected that individuals with this training will upgrade the photographic competence of the Branch, establish better professional rapport with research scientists, and provide candidates for administrative responsibilities.

Extension of the Branch's visual resource file of literature and information to serve the needs of the Branch and those of NIH investigators.

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PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS - 4
Serial Number

2. LABORATORY AIDS BRANCH

3. Dr. Robert J. Byrne
Branch Chief

I. SUMMARY

The Laboratory Aids Branch is responsible for the production of high quality laboratory rodents and rabbits; for the production of germfree animals; for the quarantine and conditioning of dogs, cats, primates and farm animals; for preparation of bacteriologic and tissue culture media and clean glassware; and for special services related to the animal sciences.

Primary efforts are made to meet the needs of the Institutes as to volume and types of animals, media or glassware. To support the basic service mission, Laboratory Aids Branch conducts research and development and animal health programs. The Research and Development program designs and tests animal caging and automated equipment for the purpose of upgrading animal care standards, making more efficient use of manpower and furnishing planning information for future facilities at the NIH Animal Center.

Animal health programs are designed to protect the quality of NIH closed colony animals and to aid in the disease control program in quarantined dogs, cats, primates, and farm animals. The latter program is a further safeguard to the health of animals in the Institute laboratories.

During the period covered by this report, Laboratory Aids Branch has accomplished its basic mission and initiated the transition to the NIH Animal Center. Occupation of Phase I construction by the Farm Animal Unit and Dog Quarantine is expected

in December 1964. Phase IA, involving the Primate Quarantine building, is in the design stages. The Program of Requirements has been drafted for Phase II but awaits a final NIH decision on the type of future Animal Production facilities for the NIH Animal Center.

Although a variety of complex scientific and logistic problems constantly face Laboratory Aids Branch, most can be and are being met through the talents and efforts of the staff. The most serious unresolved problem is that of dog and cat procurement. To protect the best interests of NIH and to upgrade the quality of animals being issued, an alternative method of production or procurement must be instituted.

II. BRANCH PROGRAMS

PRODUCTION OF LABORATORY RODENTS AND RABBITS

A. Objective

To furnish high quality laboratory rodents and rabbits by production in closed colonies under a systematic breeding program.

B. Related Programs

The production of laboratory rodents and rabbits is geared to meet Institute needs as to numbers and types of animals.

The genetics program of LAB is carried out by a staff Geneticist and four assistants. Their mission is to maintain the genetic integrity and desired features of the inbred lines of mice, rats, and guinea pigs. These characteristics are insured through the systematic use of immunogenetic testing and by maintaining a selection program. Close liaison is maintained with Institute investigators to determine suitability of issued inbred animals.

The Wing 14F cesarean-derived General Purpose mouse colony, started late in 1962, came into full production during the period covered by this report. The Wing F operation utilizes a modified barrier system and affords more security than that available in conventional B, C and E wings.

The program for producing pathogen-free animals in Wing G has been limited to the operation of one room in which animals are produced in plastic isolators. The rats and mice produced in these isolators were cesarean-derived and, at an early age, were deliberately exposed to cultures of four different species of non-pathogenic bacteria.

C. Program Progress and Accomplishments

During the Fiscal Year 1964, the Laboratory Aids Branch produced and issued over one million animals, an all time high. Many animals were bred to specific Institute requirements. For example, rabbits with specific gamma globulin characteristics were developed and produced for NIAID. In other cases, sudden demands for large volume increases were successfully met, as in the case of an unforeseen doubling in Institute needs for hamsters.

Institution of new management practices and disease control methods resulted in an excess of sales income over operating expenses. These savings were returned to the Institute animal user programs.

The Genetics Program of the Branch has fulfilled its mission during the past year by maintaining the genetic integrity and desired features of the inbred lines of animals.

Serologic tests developed by the staff Geneticist have promise of simplifying and extending the program for immunogenetic systems. Priceless strains and lines of inbred animals, not in existence elsewhere, have been maintained. A better defined mating system, designed to minimize inbreeding, has been established in the General Purpose mouse colony. A study is in progress, with favorable results thus far, to verify the mating system by working with gamma globulin isoantigens.

The position of Staff Geneticist has been vacant since July 1, 1963. LAB has been ably assisted on a part-time basis by Dr. Harold Hoffman, NCI. LAB wishes to thank Dr. Hoffman and his Chief, Dr. Walter Heston, for their help and cooperation during this period. It is anticipated that the new Staff Geneticist will report for duty by July 1, 1964.

Institute users' reactions to the quality of Wing F animals have been favorable. Significantly, the incidence of disease in the Wing F mice has been reduced considerably over the Building 12 colony from which it originated. Increased productivity and higher quality animals are the result. It is reasonable to believe that the improved barrier system, separate cage washers and increased bacteriological monitoring have been influential in producing these results.

A rat colony of the Osborne-Mendel strain was developed in a similar manner during Fiscal Year 1964 and installed in the remaining two rooms of Wing F as construction was completed. This improved colony will replace the old O-M rat colony which has long plagued Institute investigators by its high incidence of chronic respiratory infections.

The relatively small number of pathogen-free animals produced in Wing G isolators have been carefully monitored, and from the comments of Institute users, are of the highest quality. Thus far, the Wing G operation has been hampered by construction and alteration delays. On the other hand, it has furnished some valuable experience to personnel in the isolator room and, when completed, will make it possible to evaluate new construction materials and systems for future planning.

Some of the construction and renovation problems in Wing G have been solved by Plant Engineering Branch during the year. All concrete floors in the Pathogen-free area have been vacu-blasted and various types of sealed floor covering have been installed which meet the sanitation standards of Environmental Services Branch.

The Health Monitoring Program is related to many objectives described in this report and is therefore discussed elsewhere.

The Research and Development Program, while related to this objective, is described elsewhere in this report.

D. Problems

The Laboratory Aids Branch has encountered increasing difficulty during the past year in recruiting and retaining animal caretakers. An investigation of the problem revealed

that two other agencies (Army and Navy), who hire from the same certifications, utilize a wage board structure different from NIH. As a result, caretaker salaries at these agencies are considerably higher than those permitted under the NIH wage board structure. Results of the study and recommendations have been submitted to DRS.

There is an Executive Order which required that women be given equal consideration for all positions, including those requiring considerable physical strength. Although an exception to the rule was requested of the Civil Service Commission in November 1963, the request was denied. LAB anticipates possible injury compensation cases and increased use of sick leave if this problem is not resolved.

The slowness with which the Wing G Pathogen-free area construction has progressed has been very frustrating. It was originally estimated that occupancy would occur in May 1963. The current target date for occupancy is July 1, 1964.

E. Program Plans

The Pathogen-free operation will be a major program in Fiscal Year 1965. It is anticipated that full production status will be achieved by the end of the year. As the program develops, both production techniques and the engineering design of the facilities will be under continuous operational test and evaluation. As findings are developed they will be utilized for future planning purposes.

The arrival of the new Geneticist will stimulate and revitalize several research projects which had been halted in July 1963. The LAB pamphlet, Listing of Laboratory Animals Maintained by Animal Production Section, was last revised in December 1960. Since that time, nomenclatures and designations of many inbred strains have changed, additional data are now available and needed by the Institutes, and a more readable format is desired. New approaches to immunogenetic testing for integrity of strain will be investigated.

PRODUCTION OF GERMFREE ANIMALS

A. Objectives

To furnish germfree animals to NIH investigators; to develop and improve methods of producing, transferring and using germfree animals; to aid investigators in starting germfree animal projects by loaning them equipment on a short-term basis.

B. Related Programs

The germfree animal production facilities have been currently operational since August 1963 in the specially designed rooms in Building 14G. Mice and rats are produced in the germfree isolator tanks under a breeding program parallel to that employed in the conventional colonies. Cesarean derived guinea pigs are, but not bred, in germfree isolators.

The present production program is making greater use of plastic isolators in addition to the stainless steel units. The metal units will still constitute the backbone of the production colony, and the plastics will supplement this isolator space as needed. Some investigative work is being done in the plastic units.

Although no one has been able to produce a germfree hamster, the need continues. Developmental work is underway to start hamsters in the germfree environment. This work is described in the accompanying project report.

C. Program Progress and Accomplishments

While germfree animal production is now nearly in full operation in Wing G, many delays and difficulties were encountered because of design changes needed for the steam stations. Extensive testing of the new design pointed out several factors which made acceptable germfree techniques impossible. Only those changes necessary for operation were made to avoid any additional delay in the germfree animal production program.

The average monthly production of germfree animals has increased from 130 per month in 1962 to 295 per month in 1963-64. This increase started with the expanded facilities in Building 14G, available in August 1963. Deliveries from this central production point have supplied nearly all the germfree animals used by the gnotobiotic laboratories in NIDR and NIAMD. Although NIAID has been producing their own mice, LAB has supplied all of their germfree rats and is supplying an ever-increasing number of the mice they use. The strains of mice available now are NIH and BALB/c; the rats are Sprague Dawley, Fischer and Lobund.

Investigators in NCI, NIAMD and LAB's Comparative Pathology Section have taken advantage of the policy to loan plastic isolators to investigators without a germfree laboratory. The Laboratory of Physical Biology, NIAMD, has purchased some isolators of its own and relies on LAB for all of their germfree animals. The Laboratory of Viral Oncology, NCI, has used an isolator for a particular experiment and has requested one for a second experiment. The same is true with Comparative Pathology.

The success in maintaining the germfree status for production is reflected in the number of animals produced and issued. Recent laboratory tests have been negative for parasites, protozoa, fungi, yeasts, PPLO, as well as bacteria. Serologic tests for eight common mouse viruses are underway.

A cooperative effort is underway with NIAMD to study the effects of certain amino acid deficiencies in germfree and monocontaminated animals. The Unit has started determining the effects of certain vitamin deficiencies on germfree animals, and an effort is being made with NIDR to produce germfree mice on a non-antigenic diet to reduce their gamma globulin level. There are insufficient data as yet from which to draw conclusions. Although these collaborative efforts are the result of Institute requests, it is expected that LAB will benefit directly from the results.

D. Problems

Since beginning operations in August, there have been numerous interruptions of building services to install or alter the building equipment for the germfree or SPF areas. Additional

equipment shutdowns are scheduled when new or replacement items arrive for installation.

E. Program Plans

Ongoing programs will continue as outlined above.

It is anticipated that LAB will be furnishing an increasing number and variety of germfree animals.

Since plastic isolators are well adapted to short-term use, LAB will be called on more frequently to assist and advise investigators starting germfree experiments.

QUARANTINED AND CONDITIONED ANIMALS

A. Objective

To furnish quarantined and conditioned dogs, cats, primates, and farm animals to NIH investigators.

B. Related Programs

There is an established system, worked in conjunction with Procurement Section, SMB, in which LAB conducts both initial and quarterly inspections of vendors furnishing NIH with dogs and cats. Standards for sources of dog and cat supply have been upgraded. The length of quarantine period for dogs and cats has been increased to four weeks from a former requirement of only two weeks. The transportation of rhesus monkeys from India to Bethesda has been reduced 36 hours by using air service direct to Dulles International Airport.

A special flock of chickens has been maintained at NIHAC for the purpose of furnishing embryonated eggs to DBS for vaccine evaluation.

There is a program for selecting, testing, quarantining, maintaining, and culling, when necessary, farm animals at NIHAC.

The program is designed to furnish investigators with the proper type, size and species of animal to suit their needs.

Disease detection, treatment and control programs are described under Animal Health.

The Research and Development program which relates to dogs, cats, and primates is described under Research and Development.

C. Program Progress and Accomplishments

During the period covered by this report, the improved inspection system, the development of new sources of animals, and more rigid requirements for dog and cat suppliers have upgraded their standards for animal care. This factor, coupled with the increased quarantine period for dogs and cats, has increased the opportunity to secure and issue higher quality animals.

Institution of the longer quarantine period has also greatly diminished the chances of issuing to investigators an animal in the incubation period of rabies.

There were numerous logistical problems associated with doubling the dog and cat quarantine period in early 1963. The space, personnel, and supply problems were all met without reducing standards for animal care. The staff of Animal Hospital Section is to be commended for this successful effort.

Although evaluation of the improved primate transport system is as yet incomplete, it does appear that it has had a beneficial effect. In any event, it represents an advance in the humane handling of animals.

The NIHAC poultry flock has been successfully maintained free of avian leucosis virus. Thus far the flock has produced the required number of eggs and on two occasions replacement birds have been hatched and reared from surplus eggs.

One result of efforts to find the most suitable farm animal to meet the individual investigator's needs, has been the utilization of Mexican burros for producing specific antisera. The burro is more manageable than the horse, a better keeper, and is a good antibody producer. The blood serum from burros is clean and well adapted to most serologic tests.

Recent culling of sheep and goats has resulted in a more efficient use of material and manpower and given investigators a more desirable type of animal for experimental use and as a source of blood and serum.

Responsibility for the pilot dog and cat breeding program has been transferred from the Farm Animal Unit to the Dog and Cat Quarantine Unit. The program has been curtailed and results are being evaluated. Valuable information on housing, feeding and breeding practices was obtained while the project was in full operation.

D. Problems

The present system for procuring dogs and cats is unsatisfactory from the standpoint of the type, quality of animals and the methods by which they are obtained and shipped. Further, and of vital importance to the public image of NIH, is the fact that commercial sources of dogs and cats are being increasingly scrutinized by humane societies and related groups. Unfavorable publicity has resulted in the past from NIH dealing with such dog and cat vendors and can be expected in the future, despite the efforts on the part of LAB to upgrade standards specified in contracts. The difficulty stems from the fact that a dependency has developed over the years in heart and cancer research programs on a steadily increasing number of dogs and cats. It would be extremely difficult at present to procure the number and kinds of dogs and cats required under standards comparable to those which we require for rodents and rabbits in NIH colonies.

E. Program Plans

There will be several major program relocations taking place as Phase I buildings at NIHAC are occupied during the winter of 1964-65. The farm animal building and the kennel building will

become operational and this will start a series of moves in which dogs are shifted from 118A and 118B to the new kennel building and cats are shifted from Bethesda to NIHAC. Vehicles have been ordered and LAB personnel are alerted to meet the program shifts.

The Primate Quarantine Unit, which seemingly has met all demands made upon it by the NIH investigators, is undertaking a pilot breeding operation of Macaca speciosa (stump-tailed monkeys) as a further service. Primate Quarantine Unit is utilizing the stump-tailed monkey, rather than the common Rhesus, because the stump-tailed monkey reportedly becomes more docile with age as opposed to the Rhesus, and will thereby more readily adapt to a productive life in a breeding colony. This program is at the request of DBS and with their financial support. It is virtually impossible to procure neonatal primates of defined background, and exactly known age at any cost. These infants are needed in rubella studies, viral tumorigenic studies, etc., and their lack is an impediment to scientific progress.

Scientific advances will dictate demands upon LAB. Baboon organ transplants, if they prove successful, will increase the demand for procuring, conditioning, and holding of this species. There may be an increased demand for marmosets which will result in program changes including building alterations, institution of gang caging and procedures providing for high temperature and humidity.

It is anticipated that there will be an increased need from DBS and NIAID for leucosis-free chickens as a source of fertile eggs. LAB is attempting to coordinate their requests so as to plan an efficient operation in the future. At this time it is not possible to estimate the dimensions of the program.

The problem of dog and cat procurement is most sensitive. There is considerable risk and inefficiency associated with present procurement methods. NIH must turn to alternative methods to furnish the bulk of dogs and cats. Two different systems are currently being considered and explored: (1) Producing and raising dogs and cats at NIHAC on an expanded scale; and (2) contract with a penal institution or commercial source to produce and raise such animals under LAB specified standards.

DRS, Laboratory Aids Branch, cont'd:

ANIMAL HEALTH

A. Objective

To monitor the health of colony animals and to diagnose, treat and control diseases in quarantined animals.

B. Related Programs

The problem of disease control in closed colony rodents and rabbits is met through a multi-disciplined approach to monitoring. Comparative Pathology Section pathologists and microbiologists work closely with the Animal Production Section to control and eliminate infectious disease. When new disease problems do occur, maximum effort is concentrated in meeting the situations. To support health surveillance of colony animals, there is a program to study, under controlled conditions, naturally occurring diseases of laboratory rodents and rabbits.

Control of infectious diseases of primates is approached through a program of routine tuberculin testing, bacteriologic monitoring and by treatment of clinically affected animals with drugs and antibiotics.

Control of infectious diseases of dogs and cats is carried out through a program of routine immunization and by treatment of clinically affected animals with drugs and antibiotics.

Health of farm animals is maintained through a program of preventive medicine. Routine tuberculin tests are conducted on cattle. Blood tests for brucellosis are conducted on goats and cattle.

In addition to programs for controlling infectious diseases, there are studies conducted on nutritional and metabolic diseases.

Working in conjunction with the NIH Animal Nutrition Committee, LAB designs and conducts feed trials to determine the value of new rations.

One of the most valuable inbred colonies at NIH is the Strain 13 guinea pigs. A complex metabolic disease had brought

the colony to near extinction during 1962-63. The problem was investigated to determine the nature of the disease and to institute corrective or control measures. These efforts are continuing.

C. Program Progress and Accomplishments

A Bordetella bronchiseptica vaccine was prepared and used in the Strain 13 breeder guinea pigs. The vaccine has been effective in reducing pneumonia in this colony. The duration of immunity from the vaccine is at least one year.

The incidence of diarrhea in infant mice has been reduced significantly thru the use of special cage lid filters. The R&D team has recently developed an improved type of cage lid which allows more ventilation and is easy to sanitize.

It has been established that chronic murine pneumonia is probably of bacterial origin. This disease and otitis media are prevalent in the NIH colonies, but are not caused by same agents. Vaccination against chronic murine pneumonia may now be feasible.

A previously undescribed epizootic disease of rabbits was characterized. It was found to be remarkably similar to a disease of mice known for fifty years as Tyzzer's disease. Although the disease is probably bacterial in origin, the agent has not as yet been cultivated on artificial media.

Coccidiosis, a highly infectious protozoal disease, was detected in two rabbit colony rooms apparently very soon after its introduction. The disease was eliminated before it could spread to other rooms. Early detection of the disease is attributed to recent improvements in the monitoring techniques which permit rapid and thorough surveys for the presence of fecal oocysts.

A heretofore undescribed bacterium of rabbits was consistently found in large numbers in the intestines of rabbits with mucoid enteritis and found to be absent or present in small numbers in unaffected rabbits. A similar but not

identical agent of the mouse intestine, also previously undescribed, was isolated in pure culture. When this agent was injected intravenously into rabbits, the animals died 38 to 45 days later, but from a disease unlike "mucoid enteritis".

As a result of the tuberculin testing program in primates there has been a steady decline in the incidence of tuberculosis. The present rate is 1.7% as contrasted to 2.5% for calendar year 1962.

Enteric infections in primates, although still a serious problem, have been suppressed by a rigorous treatment program. Results of collaborative studies with the Division of Immunology and Infectious Disease at Walter Reed Army Institute of Research indicate a high percentage of animals infected with Shigella flexneri (serotype IV). Preliminary studies suggest that clinical manifestations can be reduced through the use of an attenuated vaccine.

Rabies has not been observed in the quarantined dogs and cats since early in 1963 when a suspicious case was observed and subsequently confirmed by fluorescent antibody test.

There has been only limited success in controlling respiratory and intestinal diseases in dogs and cats. Indirectly, the extended quarantine period has promoted the health of the animals by permitting a longer period of drug and antibiotic treatment and nutritional support. It has been difficult to measure objectively the value of vaccines and antiserums against canine distemper and hepatitis and feline distemper. Their value is definitely impaired by having to use it on animals already in the incubation period of disease, as is the case with the newly received dogs and cats.

No serious outbreaks of disease have occurred in the farm animals. Sporadic injuries have resulted from contact with the make-shift fences, gates, stalls, etc., which have been a necessary feature of construction work at NIHAC. The problem of injuries has been coped with by maintaining continuous veterinary care and routine immunization against tetanus.

Routine immunological tests on farm animals for disease as prescribed by Maryland State or Federal law have been negative for brucellosis and tuberculosis.

Progress on nutritional and metabolic diseases has been as follows:

Feed trials designed by the NIH Animal Nutrition Committee and conducted by LAB revealed that a hi-fat diet resulted in less eaten litters of mice but more infant diarrhea. In contrast, mice on a simplified diet had less diarrhea but there were more eaten litters.

Since 1962-63 the Strain 13 guinea pig colony has been restored to normal status following an emergency investigation which revealed dietary deficiencies as well as a dietary toxicity. The investigation revealed that animals of all ages were dying of a variety of conditions not directly attributable to infection by microbial agents. The primary cause of death in young animals was non-specific diarrhea and in breeder animals was pregnancy toxemia and metastatic calcification. The investigation indicated that (1) the commercial ration fed to the guinea pigs failed to provide optimal growth and reproduction requirements when fed without supplementation, (2) the high incidence of pregnancy toxemia was due to the occurrence of stress in nutritionally pre-disposed animals, and (3) metastatic calcification was caused by a toxic level of Vitamin D in the commercial ration.

D. Problems

Laboratory Aids Branch is in need of an additional pathologist in Comparative Pathology Section. The only participating anatomical pathologist at the present time is also Chief of the Section. Although a position is available, it has been formally obligated to an NIH employee who will not return from graduate school until FY 1966. A request to open a new position was denied for budgetary reasons.

E. Program Plans

Ongoing programs as outlined in B. will continue.

DRS, Laboratory Aids Branch, cont'd:

It is anticipated that with the approval of Building 28A renovations, a more intensive effort can be made to study chronic murine pneumonia, Tyzzer's disease and mucoid enteritis of rabbits.

RESEARCH AND DEVELOPMENT

A. Objectives

To conduct, in collaboration with RFPB, a Research and Development Program designed for improving animal facilities, caging and automated feeding, watering and sanitary systems. To investigate environmental factors influencing animal production. Both of these objectives are part of the overall mission to provide NIH investigators with the best animals possible.

B. Related Programs

Basically, the LAB/RFPB R&D Programs were established to fulfill the objectives stated above and, in addition, to upgrade standards for animal care, make more efficient use of manpower, and to furnish basic information which could be incorporated into planning for the NIH Animal Center.

There are three general types of R&D programs:

1. Products and Materials Testing - In this program, needs are first determined and the market is searched for available commodities. Available products or materials are obtained and evaluated.

2. Developmental - Needs are first determined, and, if satisfactory items are not available commercially, rough sketches and functional requirements are prepared for contracting. The contractor then designs and/or engineers the item, prepares tentative drawings and, if feasible, builds a prototype. Test and evaluation is then conducted by the R&D Team in the appropriate Section of LAB. Quite frequently, needed modifications are worked in during the period of testing.

Developmental studies have been carried out on automated rabbit batteries, dog cages for NIHAC, mouse box filter lids and modular general purpose batteries for guinea pigs and rats.

3. Factors Research - Projects in this category relate to the study of environmental factors which are believed to influence productivity in laboratory rodents and rabbits. A special room with six cubicles has been constructed in which mouse production is now being studied under controlled light cycles. Experiments are designed to determine the effect of different day lengths on productivity.

C. Program Progress and Accomplishments

Products and Materials Testing - During the period covered by this report the R&D Program has related closely to the development of the Pathogen-free area in Wing 14G and NIHAC Phase IA and Phase II. A central vacuum cleaning system was installed in the 14F-1 cagewashing area for the F and G wings. This will enable evaluation studies contrasting the methods of cleaning in the animal rooms as in Wing G with a central cleaning facility in the cagewash area. The results of this evaluation, when complete, will enable future planning for NIHAC Phase II and may indicate that the more economical method of the centrally located system is satisfactory for LAB purposes. Six different floor coverings were installed during this period in the 14G wing. Each of these floor coverings will be evaluated from a standpoint of wear, sanitation, and applicability to determine which material should be used at NIHAC Phase II. In the Wing G Pathogen-free area a need arose to develop a means of filling water bottles from the sterile water supply without contaminating the water or the bottles. One commercially available unit was purchased and found unsuitable for the particular type of operation. Modifications were indicated and the item was switched to the developmental area. From this evolved a very satisfactory model at a cost of $45 in contrast to the unacceptable commercial model which sold at over $300 per unit. Many other items were obtained during the year to meet specific needs, evaluated, and turned over to the appropriate Section for bulk purchasing for their operations.

Developmental Projects - As indicated earlier, developmental projects are undertaken only when the need cannot be satisfied from a commercially available source. During the period of this report, probably the most significant accomplishment was the development of an automatic sipper tube and water bottle washer for Wing F. Working with the Girton Manufacturing Company as contractor, the R&D Team developed a machine which empties the water bottles coming from the room, washes the sipper tubes and bottles separately, sterilizes each and refills the bottles at the other end of the machine with sterile water which has been adjusted to a pH of 2.5 with hydrochloric acid. The filled units are then returned to the animal rooms for application to the cages. Three automated batteries for use at NIHAC in Phase II have been developed during the period of this report, evaluations have been completed on the unit for one species and modifications have been made to the prototype which is under test. Drawings for the automated modular general purpose battery have been completed and prototype contracts are now in progress. Dog holding cages were designed and prototypes constructed for the animal building at NIHAC Phase IA. These are now under evaluation by the Animal Hospital Section.

Factors Research - Construction on the controlled environment cubicles was completed by the contractor in February 1964. Equipment shakedown with test animal load has been completed. First year-long experimental run will begin on or about July 1, 1964.

D. Problems

The major problem encountered by the LAB/RFPB R&D Team during Fiscal Year 1964 was the fact that both members of the team were involved in additional duties which required a considerable amount of time. As the program progressed, it also became evident that there is a need for a technician to assist in the evaluation and operation of the many prototypes which are now beginning to evolve as a result of this program.

Another problem which leads to inefficiency and requires the maintenance of two separate sets of records, files, and contractor difficulties is the physical separation of the two members of the

R&D Team. It is believed the operation would be much more efficient if the RFPB Team member could be housed in the LAB area.

E. Program Plans

A busy program is anticipated for FY 1965 as planning for NIHAC Phase II gains impetus. Both R&D Team members will be able to devote more time to projects. There will be several major projects, outlined below, plus solving routine LAB operational problems as they arise.

With the first species to move to NIHAC in mind, a major program of installation, evaluation and modification of the prototype modular general purpose battery for rats will get underway. This will be coupled with an automatic rat stock watering system evaluation.

Close liaison will be maintained with RFPB during the year to parallel progress on NIHAC IA, and II. Phase II POR's, mechanical and functional, will be completed and by the end of the year should include work with the A/E.

The first year operation of the Pathogen-free area will require the services of the R&D Team to solve problems arising during the "shake-down" period. Past experience indicates problems of both a mechanical and physiological nature.

The obsolete cage drawing and specification revision program in collaboration with SMB will be continued. This involves all caging used by the Institutes as well as LAB and will result in better products at a lower cost for Institute users.

MEDIA PRODUCTION

A. Objective

To produce and issue the highest quality bacteriological and tissue culture media. To furnish consultative services to the Institutes on related problems.

B. Related Programs

Media production is geared to meeting Institute needs as to volume and type of media. To fulfill its mission, the Media Unit employs automated equipment wherever possible and makes use of an efficient cross-reference system of record keeping.

The quality control program of media production was enhanced by the addition of tissue culture laboratory work space in June 1963. The Media Preparation Unit is now able to furnish concurrent testing of its media in established tissue culture cell lines.

The Media Unit assists in the development of improved methods for procuring and storing blood, serum, tissues, etc., from animal sources. The Unit also tests and processes these materials for issue or incorporation into media or tissue culture.

C. Program Progress and Accomplishments

Based on the fifteen month period from January 1963 through March 1964, the projected number of requisitions for eighteen months will total 18,000. In contrast the monthly average for 1962 was 955.

In terms of volume of media produced, the figures for the fifteen months above show 44,000 liters of tissue culture media and 58,000 liters of bacteriological media. These figures projected for the full eighteen-month reporting period indicate a total volume of 122,000 liters of all types of media produced.

During this reporting period investigator complaints received have been at a minimum. It is particularly gratifying to report that the bacteriologic sterility rate for blood plates has increased to an average of 97%.

As a by-product of the expanded quality control program, a number of different tissue culture cell lines were added to the frozen cell bank maintained in the Unit. These cell lines, obtained free of Pleuropneumonia-like organisms (PPLO) from other investigators or freed of PPLO by the Unit, and then frozen

away, have on several occasions served as a source of supply for other investigators having difficulty with their own cells.

In putting up cells for quality control purposes, it has been possible with slightly more effort to increase the number of tubes of cells prepared on a weekly basis. These cells have been issued to an increased number of interested investigators in several Institutes for their evaluation. In every instance, the investigators have continued to report complete satisfaction with the cells they had received.

During the year a problem arose involving the occurrence of an excessively high pH in numerous lots of tissue culture media dispensed and stored in Kimler-Wheaton bottles. In some cases the subsequent loss of media ran as high as 25% of a given lot. In cooperation with the Wheaton Glass Company the cause was traced to the constant reuse of the caps, whose liners become hard and lose their resiliency after several autoclave cycles, giving an imperfect seal. The problem has been solved temporarily by using a new cap each time. Negotiations are underway to find a different rubber liner which will hold up under several sterilizations.

The occasional problem of contamination in sheep blood received from the NIH Animal Center appears to have been solved by modifications in the bleeding technique and blood container. Since the changes were put into effect there has not been a single case of contaminated blood.

D. Problems

Although it appears that space outside of the Media Unit will not be made available, the need for such space still exists. The present space occupied by the Unit was originally designed to be used only as extra storage space for the Clinical Center. Although many minor modifications of this space have been made, there has always been a problem of periodic contamination. Most of these contamination problems can be traced to the lack of adequate sterile preparation areas and to overcrowded conditions in areas presently used for sterile production. Ideally, sterile production should be carried out in small, easily cleaned sterile rooms with a minimum amount of traffic and disruption during the

critical time of aseptic dispensing of sterile media. We still do not have these conditions in either tissue culture media or plate pouring production areas, and until these conditions are met the quality of the media produced will be affected. Hopefully, the current DRS-sponsored space utilization study will result in the development of solutions to these problems.

The lack of adequate containers vital to production in the Unit is a continuing problem. These containers, such as metal section baskets for dispensing, sterilization, and delivery of tubed media; and large metal trays for transport of large flasks of media, are always in short supply. Without a steady flow of these containers it is impossible for the Unit to meet the demands of the investigators or to guarantee the condition of the media by the time it reaches the laboratory.

E. Program Plans

Ongoing programs described under part B will be continued.

The demand for tissue culture cells of various types is expected to increase among the interested investigators using these cells. Within the limits of present personnel and space for this type of service, an attempt will be made to keep pace with this demand.

It is anticipated that upon completion of exhaustive tests both in the Media Unit and by other organizations on dehydrated complete tissue culture media, there will be increased use of this material in place of individually weighed and prepared media of various types.

GLASSWARE PREPARATION

A. Objectives

To furnish clean glassware of the highest quality by processing through the steps of decontamination, cleaning, wrapping, sterilization and issue. This overall operation includes processing of used glassware from the investigators

and the introduction of new glassware from adequately maintained replacement stock.

To furnish consultative services on problems associated with laboratory glassware.

To furnish cagewashing service to the Clinical Center, Auburn Building, and Patuxent River Laboratory.

B. Related Programs

In addition to filling Institute demands for the volume and types of glassware, the Unit evaluates management and technical methods and equipment for improving the quality and maintaining the volume of issued glassware.

The cagewashing unit furnishes the services cited under A. above and studies problems associated with corrosion, scaling, etc.

C. Program Progress and Accomplishments

Projected through June 1964, there will have been 9,200,000 pieces of laboratory glassware issued to the various Institutes since January 1963. In addition, the three Institutes or Divisions that do not contribute to the replenishment fund at present will have received another 706,000 pieces of glassware. The total actually would run over 10,000,000 if the glassware used within the Media Unit were counted. These figures represent an increase of about 7% over the last reporting period.

The Glassware Preparation Unit has continued to maintain close contact with the investigators and work in close cooperation with them to resolve temporary problems regarding quality or quantity of glassware issued.

The purchase of new resins for the present deionizers this year has greatly extended their usefulness. Also, it is fortunate that the heavy snow and rainfall of the past winter has reduced the total hardness of the raw water supply to such an extent that the present deionizers are getting over 100% more capacity per regeneration.

Temporary measures were taken this year to insure a satisfactory final rinse for pipettes. The pipettes from both machines presently in use are being rinsed in a new unit which has been installed between them. This method eliminates hand rinsing of the pipettes, but does reduce slightly the number of pipettes that can be processed each day. It is hoped that the two new machines which have been requested can be made and installed during the coming year.

Since taking over the complete responsibility for gas sterilization, the demands for this service have increased considerably. The large unit has operated an average of three times a month, while the smaller units are run as many as three times a week.

A projected total of 507,000 cages, racks, cans, feeders, etc. will have been processed by the end of June 1964. This is a drop of about 15% compared with last reporting period despite an increase in cages and racks from the Auburn Building and from the Patuxent River Laboratory.

D. Problems

In the Glassware Unit as well as in the Media Unit there remains a continuing critical shortage of metal containers vitally important to production. These include glassware storage and sterilizing baskets, and dirty glassware trays for return of used glassware from the investigators. The lack of adequate numbers of the dirty glassware trays is probably the biggest single reason for inability to keep up with demand for glassware. If the investigator has no container to dispose of used glassware for subsequent return for processing, the flow pattern is interrupted with an accompanying backlog of requests.

The Unit has been somewhat hampered during the entire reporting period by at least two vacancies at all times. While the Unit is able to meet most of the requirements of the investigators, the general housekeeping of the area including machines, tables, sinks, etc. has suffered. Again, it is recommended that the possibility of increasing the maximum grade level for employees in the Glassware Unit at least one grade be seriously considered. This would not only reward the employees

of the Unit for their consistent work, resulting in a steady increase in production, but also would enable the Unit to keep an adequate number of trained employees.

There are several safety hazards associated with the operation of the Glassware Unit which continue to be a problem. The lack of, or improper decontamination of, used glassware before return to the Unit for processing is a constant threat to the safety of the employees working in this area. Also, the removal of screw caps from used tubes with the present equipment has resulted in a number of bad hand cuts for employees assigned to this task.

E. Program Plans

A project planned for some time by the Glassware Unit and now slated for the immediate future is the conversion to disposable glass culture tubes. There are four main advantages to this conversion. They are:

1. The virtual elimination of the tube sorting area, releasing one employee for other duties;

2. The elimination of practically all soaking tubs, freeing additional floor space;

3. The speeding up of the loading of tubes in the washing baskets; and

4. Inspection of tubes will be reduced to a formality and laboratory results will be more easily and accurately read.

A project to automate the wrapping of pipettes and speed up the present mechanical plugging of culture tubes has been started. Specifically, the Instrument Engineering and Design Branch is looking into the feasibility of modifying a commercially available paper straw wrapper to enable it to wrap pipettes. The Kimble Glass Company is attempting to modify a pipette plugging machine to enable it to accommodate culture tubes and plug them at a much higher rate of speed than our present machines. To date, there has not been any progress reported on either item.

It is anticipated that a new deionizer will be purchased, installed and put into use within the next year. If proper ancillary safeguards are provided it is anticipated that it will improve the quality of H_2O for central sterile supply, media and glassware washing.

SPECIAL AND CONSULTATIVE SERVICES TO THE INSTITUTES

A. Objective

To furnish special services to the Institute investigators and to NIH including: Consultation on animal health and related fields; animal X-ray and surgery; and planning of animal facilities to comply with accepted standards and to meet the needs for the projected use of the building.

B. Related Programs

The Laboratory Aids Branch veterinarians, microbiologists, animal husbandmen and other specialists furnish NIH investigators with a variety of information on normal animal anatomy and physiology, proper husbandry practices and disease problems.

Animal X-ray and surgical services are maintained in Building 28. A trained staff in the Animal Hospital Section furnishes these services to NIH investigators on a first-come first-served basis. The surgical services are supported by a postoperative care program and long-term holding facilities.

Representatives of Laboratory Aids Branch develop Programs of Requirements for their own facilities such as the NIH Animal Center and evaluate the A/E drawings. The Branch is also consulted on the planning of other NIH facilities in which animals are to be produced, housed or used.

C. Program Progress and Accomplishments

Although results are not readily measurable, the consultative service furnished by LAB to the NIH investigators undoubtedly assists in helping in the design and evaluation of animal experiments. The Comparative Pathology Section is probably called on

most frequently to furnish information on the normal and abnormal characteristics of a variety of laboratory animals.

The surgical and X-ray services have enabled NIH surgeons to increase their volume of surgical procedures with a minimum of wasted effort on their part. The postoperative care and high standards of long-term holding have contributed to the survival rate of dogs which are extremely valuable as a result of having had inserted in their bodies heart valves, prosthetic devices, etc. X-ray service is an essential adjunct to the surgical service and in addition is used for a variety of other diagnostic and research purposes. Veterinary consultation service on X-ray and surgery has been of valuable assistance to the investigators.

The planning and design of new NIH animal facilities has been greatly aided by the experience gained by LAB during its occupation of Buildings 14 and 28. Other vital information worked into new construction planning and design is that obtained and evaluated as results of visits to other outside animal facilities by LAB and the LAB/RFPB R&D team representatives.

D. Problems

Although many of the aspects of this service are time consuming, they are regarded as a vital part of LAB's mission. An obvious gap in NIH animal services is in the lack of defined centralized control on the outside purchase of animals and in setting and maintaining standards for animal care in the Institutes. Among other things, this has, in the past, resulted in the introduction of animal infections into Institute laboratories.

E. Program Plans

The programs will continue as outlined in section B.

The objectives remain the same, but it is recommended at this point that the Division of Research Services consider the basic problem outlined in section D and in future discussions consider implementing a stronger NIH-wide animal program.

PUBLICATIONS AND PATENTS

Publications

Allen, A. M.: Conference on Mast Cells and Basophils "Round Table Discussion." Ann. N. Y. Acad. Sciences. 103: 462-464, Feb. 1963 (comments and photographs contributed).

Every, R. R., Menges, R. W., and Habermann, R. T.: Canine blastomycosis in Louisiana. Delta Vet. 6: 15-16, 3rd Quart. 1963.

Gay, W. I.: Prosthetic replacement of the femoral head. Proc. World Vet. Cong. 2: 1087-1093, Aug. 1963.

_____ and Moore, S. J.: Conjunctival flap for surgical treatment of epithelial plaques in the bovine eye. J. Amer. Vet. Med. Ass. 143: 1000-1003, Nov. 1963.

Habermann, R. T., and Williams, F.P., Jr.: Papillary cystic adenocarcinoma of a kidney in a dog. J. Amer. Vet. Med. Ass. 142: 1011-1014, May 1, 1963.

_____ and _____: Treatment of female mice and their litters with piperazine adipate in the drinking water. Lab. Anim. Care 13: 41-45, Feb. 1963.

_____, _____, McPherson, C. W., and Every, R. R.: The effects of orally administered sulfamerazine and chlortetracycline on chronic respiratory disease in rats. Ibid. 13: 28-40, Feb. 1963.

Jaworski, N. A., and Miller, C. E.: Refinement of the cylinder technique for supplying germfree plastic isolators. Ibid. 13: 591-601, Aug. 1963.

McPherson, C. W.: Reduction of Pseudomonas aeruginosa and coliform bacteria in mouse drinking water following treatment with hydrochloric acid or chlorine. Ibid. 13: 737-744, Oct. 1963.

DRS, Laboratory Aids Branch, cont'd:

Menges, R. W., Habermann, R. T., Selby, L. A., and Behlow, R. F.: Histoplasma capsulatum isolation from a calf and pig. Vet. Med. 57: 1067-1070, Dec. 1962.

_____, _____, _____, _____, and Smith, C.D.: A review and recent findings on histoplasmosis in animals. Ibid. 58: 331-338, April 1963.

Moore, S. J., Gay, W. I., and Penney, B. E.: A self-contained fluid administration pack for dogs. Lab. Anim. Care 1: 33-35, Feb. 1964.

Serial No. 4.1

1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: EFFECT OF HYDROCHLORIC ACID AND CHLORINE TREATMENT UPON PSEUDOMONAS AERUGINOSA AND COLIFORM BACTERIA IN MOUSE DRINKING WATER

Principal Investigator: Charles McPherson, D.V.M.

Other Investigators: Damara Bolte', B.S.

Cooperating Units: None

Man Years (computed for the 18-month period):

Total:	less than .1
Professional:	--
Other:	--

Project Description:

Objective: To find a water additive which would inhibit bacterial growth, especially that of Pseudomonas aeruginosa, in animal drinking bottles.

Methods Employed: Cages containing infected mice were divided into two groups. For each group two water bottles were put on each cage, one with tap water, and one with either tap water plus HCl or tap water plus sodium hypochlorite (chlorine) solution. Each water bottle was tested for the presence of P. aeruginosa and coliforms every day for seven days.

Major Findings: Both HCl and chlorine were effective, but HCl was not as rapidly dissipated.

Significance: Contaminated animal drinking bottles are an important reservoir and vehicle in the transmission of P. aeruginosa and other infectious agents in animal colonies. Accordingly, an additive to prevent such contamination is important. As a result of the findings of this study several colonies of mice are routinely given HCl treated drinking water.

Proposed Course of Project: Completed.

Part B included Yes X No

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

McPherson, C. W.: Reduction of Pseudomonas aeruginosa and coliform bacteria in mouse drinking water following treatment with hydrochloric acid or chlorine. Lab. Anim. Care 13: 737-744, Oct. 1963.

Honors and Awards relating to this project:

None

Serial No. 4.2

1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: A COMPARISON OF TWO DIETS FOR MOUSE PRODUCTION

Principal Investigator: Charles McPherson, D.V.M.

Cooperating Units: None

Other Investigators: None

Man Years (computed for the 18-month period):

Total:	less than .1
Professional:	--
Other:	--

Project Description:

Objective:	To find which of two feed formulations resulted in better mouse production.
Methods Employed:	Each feed was fed to an entire room of mice. All other conditions were controlled. Production and mortality rates were measured for a 9-month period.
Major Findings:	Total production differed little between the two formulas. However, mice fed the Hi-Fat formula had more litters with diarrhea while mice fed the Simplified formula had more eaten litters.
Significance:	Tests of this type are necessary to determine which feed formulae result in high mouse production.
Proposed Course of Project:	The first phase of study was completed in March 1963. Beginning in July 1964, an attempt will be made to alter the Simplified formula to reduce the number of eaten litters.

Part B included: Yes_____ No X

Serial No. 4.3
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: COOPERATIVE LAB-ESB STUDY OF PSEUDOMONAS AERUGINOSA IN ANIMAL WATER BOTTLES

Principal Investigators: Charles McPherson, D.V.M.
Warren Powell, M.S., ESB, DRS

Other Investigators: Wilmer Dockstader, Ph.D., ESB, DRS
James Cox, M.S., ESB, DRS
Lloyd Herman, Ph.D., ESB, DRS

Cooperating Units: Environmental Services Branch

Man Years (computed for the 18-month period):
Total: .15
Professional: .075
Other: .075

Project Description:

Objective: To explore several methods of cleaning and handling water bottles to control P. aeruginosa infection in animal colonies.

Methods Employed: Two rooms of NIH strain mice were divided into five test areas each. The control methods tested were HCl treatment of drinking water, ultrasonic cleaning followed by chlorine rinse of drinking bottles and tubes, autoclaving of filled and stoppered bottles, autoclaving of sipper tubes only, and a control group. Each week a random sample of about 26% of the water bottles was cultured to check for the presence of P. aeruginosa. The study lasted 10 weeks.

Major Findings: HCl treatment of drinking water reduced P. aeruginosa contamination to zero during the test period, but as soon as treatment was discontinued contamination rates immediately rose to former levels. Other methods tested were ineffective.

Part A (Cont'd)

Significance: Contaminated animal drinking bottles are an important reservoir and vehicle in the transmission of P. aeruginosa and other infectious agents in animal colonies. Accordingly effective control methods must be found.

Proposed Course of Project: Further studies should be conducted under strict environmental control.

Part B included: Yes_____ No__X__

Serial No. 4.4

1. Laboratory Aids Branch
2. Germfree Animal Production Unit
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: ESTABLISHING AND PRODUCING GERMFREE HAMSTERS

Principal Investigator: Carl E. Miller, D.V.M.

Other Investigators: Howard J. Bohner, B.A.

Cooperating Units: Animal Production Section, LAB

Man Years (computed for the 18-month period):

Total:	.25
Professional:	.10
Other:	.15

Project Description:

Objective: To establish hamsters in the germfree environment and maintain them by production in the germfree isolators.

Methods Employed: The usual cesarean delivery of the infants and attempting to raise them by either hand feeding or foster nursing on other species of germfree mothers.

Major Findings: The very small size and immaturity of the infant hamster (16-day gestation period) makes replacing its mother very difficult. A method of obtaining hamster milk and sterilizing it without heating has been developed. One newborn hamster was raised outside of an isolator. This has not been duplicated since.

Significance: The importance of hamsters in disease research has increased a great deal with the reports of the hamster's susceptability to adenoviruses and that SV-40 produces tumors in their cheek pouches. The germfree hamster will eliminate any complicating infections in this type of experimental work. Also, this type of hamster will be used in the dental caries work.

Proposed Course of Project: Continuation.

Part B included Yes____ No X

Serial No. 4.5
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: BREEDING OF THE STUMP-TAILED MACAQUE MONKEY (MACACA SPECIOSA) IN CAPTIVITY

Principal Investigator: Amos E. Palmer, D.V.M.

Other Investigators: Ruth Kirschstein, M.D., DBS
William Tullner, Ph.D., NCI

Cooperating Units: Division of Biological Standards
National Cancer Institute

Man Years (computed for the 18-month period):
Total: .3
Professional: .15
Other: .15

Project Description:

Objective: To attempt to find the reproductive potential of Macaca speciosa in captivity. To produce infant M. speciosa for research. To introduce a primate species into NIH laboratories which is more easily handled than the rhesus monkey (Macaca mulatta).

Methods Employed: Menstrual cycles will be ascertained and matings attempted at the expected time of ovulation. Births will be recorded and infants used in research.

Major Findings: Project has only begun. No major findings at present.

Significance: With the present trend toward refined research techniques, it is essential that laboratory animals become more defined. Present primate sources are unable to produce more defined animals, thus breeding in captivity is necessary. It is desirable to use animals which are more easily handled and which create less hazards to investigators and animal caretakers. The Macaca speciosa will fulfill these qualifications if breeding on a economic basis is possible.

Part A (Cont'd)

Proposed Course of Project:	Continuation or discontinuance will be determined based on results.
Part B included	Yes_____ No X

Serial No. 4.6

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: THE GENERATION TIME OF MAST CELLS OF THE RAT

Principal Investigator: Anton M. Allen, D.V.M., Ph.D.

Project Description:

Proposed Course of Project: Project in suspension, due to lack of time and personnel.

Part B included Yes X No

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Allen, A. M.: Conference on Mast Cells and Basophils "Round Table Discussion." Ann. N. Y. Acad. Sciences. 103: 462-464, Feb. 1963 (comments and photographs contributed).

Honors and Awards relating to this project:

None

Serial No. 4.7
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: ACUTE EPIZOOTIC PNEUMONIA IN THE GUINEA PIG COLONY

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.

Cooperating Units: Animal Production Section

Man Years (computed for the 18-month period):
Total: 1.1
Professional: .7
Other: .4

Project Description:

Objective: To elucidate the etiology of acute epizootic pneumonia which occurs in the guinea pig under colony conditions. To devise an effective method for its prevention.

Methods Employed: Routine microbiology, pathology, immunology, and epidemiology methods were used.

Major Findings: The cause of the pneumonia was found to be Bordetella bronchiseptica. The carrier state, which could be detected only at necropsy, complicated preventive measures. Sulfonamides, administered in the drinking water, were effective in controlling losses but did not prevent the carrier state. A single intramuscular injection of bacteria in oil emulsion resulted in complete protection, development of sustained high levels of serum antibody and elimination of the carrier state.

Significance: Future existence of the highly inbred Strain 13 production colony was in jeopardy. The heretofore recommended procedure for controlling epizootic Bordetella bronchiseptica pneumonia in the guinea pig colony was to sacrifice and start anew, breeding from clean animals. This procedure could not be entertained. The inception of the vaccine procedure to breeders only has stopped all losses due to pneumonia and has restored the production capacity of the colony to its normal level.

Part A (Cont'd)

Proposed Course of Project:	Completed. A manuscript on this project is in preparation.
Part B included	Yes_____ No__X__

Serial No. 4.8
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: CHRONIC MURINE PNEUMONIA OF THE ALBINO RAT

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.

Cooperating Units: None

Man Years (computed for the 18-month period):
Total: .6
Professional: .2
Other: .4

Project Description:

Objective: To isolate and characterize and etiologic agents. To perform transmission studies with each suspected agent. To recommend measures for prevention and control of this disease complex under colony conditions.

Methods Employed: Microbiology, immunology, and pathology methods were employed.

Major Findings: Results of studies to date indicate that the etiology is of bacterial nature rather than viral as proposed by other investigators heretofore. Controlled vaccine studies are in progress in the General Purpose rat colony. Studies also indicate that the etiology of otitis media is separate and distinct from that of the pathological processes observed in the lower respiratory tract.

Significance: This disease complex is the greatest cause of morbidity and eventual mortality in rat colonies. Affected rats are unfit for research, particularly when destined for long term or toxicity studies.

Proposed Course of Project: Continuation.

Part B included Yes_____ No X

Serial No. 4.9
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: MUCOID ENTERITIS OF RABBITS

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.
Thomas D. Moore, Ph.D.

Cooperating Units: Animal Production Section

Man Years (computed for the 18-month period):
Total: .9
Professional: .6
Other: .3

Project Description:

Objective: To determine the etiological factor(s). Attempt experimental reproduction of the disease in rabbits. Based on the foregoing, to recommend measures for control or prevention in the rabbit colonies.

Methods Employed: Routine pathological and bacteriological methods were used.

Major Findings: This chronic condition in weanling rabbits smolders endemically in the rabbit colonies. Although sporadic in occurrence, when it does appear, usually the entire litter is affected. While pure culture isolation has not been possible as yet, a heretofore undescribed microorganism has been observed in roughly 95% of the cases. Attempts to culture this organism are still in progress. To date, it cannot be stated that the causative agent for mucoid enteritis has been identified.

A similar but not identical agent of the mouse has been isolated in pure culture. The agents from both the rabbit and the mouse occur in the cecum and proximal colon and have highly characteristic morphology and tinctorial properties. The agent from the mouse is slightly smaller than the one from the rabbit. This agent selectively grows in the cytoplasm of hepatic cells of intravenously inoculated rabbits and results in extensive liver necrosis and death in 40-45 days.

Part A (Cont'd)

Significance:	Mucoid enteritis is the greatest cause of morbidity in our rabbit colonies. Though widely recognized as such throughout the world, etiology has not been ascertained.
Proposed Course of Project:	Continuation.

Part B included Yes_____ No__X__

Serial No. 4.10

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: STUDY OF CAUSES OF DEATH IN STRAIN 13 AND STRAIN 2 INBRED GUINEA PIG COLONIES

Principal Investigator: James R. Ganaway, D.V.M., M.P.H.

Other Investigators: Anton M. Allen, D.V.M., Ph.D.
Roy Kinard, D.V.M.

Cooperating Units: Genetics Unit, LAB

Man Years (computed for the 18-month period):

Total:	1.5
Professional:	.9
Other:	.6

Project Description:

Objective: To define the causes of losses in the inbred colonies of guinea pigs. To isolate the etiologic agent(s). To recommend measures for control or prevention of these losses in the colonies.

Methods Employed: Routine microbiology, pathology (both clinical and anatomic), nutritional, and epidemiology methods were used.

Major Findings: Results to date indicate that unidentified dietary deficiencies and Vitamin D toxicity were primarily involved in the rapid deterioration of the colonies. Supplementation of the diet with green leafy plants and reduction in the intake of Vitamin D resulted in complete restoration of the colony.

Significance: Strain 2 and Strain 13 guinea pigs are among the most valuable at NIH and are not available from outside sources. During 1962-63, the breeding colonies of these animals deteriorated to a point of near extinction as a result of increased incidence of disease.

Proposed Course of Project: Continuation. Several areas of interest derived from this study will be pursued further.

Part B included Yes____ No__X__

Serial No. 4.11

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: A SURVEY OF MYCOTIC DISEASES IN DOMESTIC ANIMALS SUBMITTED BY THE COMMUNICABLE DISEASE CENTER, KANSAS CITY, KANSAS

Principal Investigators: Robert T. Habermann, D.V.M.
Robert W. Menges, D.V.M., M.P.H., CDC

Other Investigators: Rex R. Every, D.V.M. (now at Paige Animal Hospital)

Cooperating Units: Communicable Disease Center

Project Description:

Proposed Course of Project: Suspended.

Part B included Yes X No

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Menges, R. W., Habermann, R. T., Selby, L. A., and Behlow, R. F.: *Histoplasma capsulatum* isolation from a calf and pig. *Vet. Med.* 57: 1067-1070, Dec. 1962.

_____, _____, _____, _____, and Smith, C. D.: A review and recent findings on histoplasmosis in animals. *Ibid.* 58: 331-338, April 1963.

Honors and awards related to this project:

None

Serial No. 4.12

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: ESTIMATION OF ALLANTOIN IN BODY FLUIDS OF ANIMALS

Principal Investigator: Silas Jackson, M.S.

Other Investigators: Roy Kinard, D.V.M.

Cooperating Units: None

Man Years (computed for the 18-month period):
Total: .1
Professional: .1
Other: 0

Project Description:

Objective: To develop a reliable procedure for the estimation of allantoin in animal urine and blood.

Methods Employed: Ordinary methods and techniques of paper and thin layer chromatography, elution, color development and colorimetric analysis were employed.

Major Findings: (1) Allantoin can be made to migrate on certain paper and thin layer chromatographic systems with suitable R_f values. (2) On systems tested allantoin separated from certain contaminating substances. (3) Allantoin so purified may be eluted and quantitated colorimetrically.

Significance: Uric acid values of serum or urine are useful in the diagnosis of certain types of renal disfunction. Most animals other than man and chimpanzees degrade significant amounts of uric acid to allantoin. Uric acid and allantoin values therefore must be combined for diagnostic usefulness. Other procedures for the estimation of allantoin did not carry out a physical or physicochemical separation of allantoin from its contaminants but depended upon the specificity of an oxidation reduction color development reaction. It is possible that this final color may be enhanced by the reducing substances other than allantoin found in urine and plasma. This procedure utilizes a separation of allantoin from its contaminants prior to color development.

Part A (Cont'd)

Proposed Course of Project:	Continuation.
Part B included	Yes_____ No__X__

Serial No. 4.13

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: INDUCTION OF RETICULOCYTE RESPONSE IN GOATS

Principal Investigator: Roy Kinard, D.V.M.

Other Investigators: None

Cooperating Units: Animal Hospital Section

Man Years (computed for the 18-month period):
Total: .2
Professional: .1
Other: .1

Project Description:

Objective: To induce, confirm, and evaluate the reticulocyte response of the goat, which, like most farm animals, does not normally release reticulocytes into peripheral blood.

Methods Employed: Ordinary hematological methods were employed. Anemia was induced by daily bleeding.

Major Findings: Anemia led to proportional reticulocyte release, as in mammals in general. Degree of anemia and time required to cause various percentages of reticulocytes were established. These data will be used as baseline information in future studies.

Significance: Textbooks are vague on reticulocyte responses in farm animals, so confirmation of reticulocyte release in anemia was needed if we were to use this test for diagnosis. The information is also basic to certain proposed studies of the physiology of reticulocyte release.

Proposed Course of Project: This project is terminated. Any continuation will be under a different title.

Part B included Yes_____ No X

Serial No. 4.14

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: INVESTIGATION OF A MEANS FOR CLINICAL DIAGNOSIS OF CHRONIC RESPIRATORY DISEASE OF RATS

Principal Investigator: Roy Kinard, D.V.M.

Other Investigator: James R. Ganaway, D.V.M., M.P.H.

Cooperating Units: None

Man Years (computed for the 18-month period):
Total: .5
Professional: .2
Other: .3

Project Description:

Objective: To evaluate gamma globulin level as an indication of presence and severity of chronic pneumonia of rats and to use this indicator, if valid, as an aid in diagnosis, control, and study of the disease as it occurs in NIH colonies.

Methods Employed: Ordinary methods of autopsy, histopathology, serum protein electrophoresis and statistics have been used.

Major Findings: The rats of the NIH production colonies have a very high incidence of chronic respiratory disease accompanied by high gamma globulin levels. Rats with low gamma globulin, and considered free of CRD, developed the disease and high gamma globulin after exposure to diseased rats. Control rats that remained free did not show the globulin rise. Statistical evaluation, to determine whether severity of lesions and gamma globulin levels are proportional, has not been completed.

Significance: Chronic respiratory disease occurs in nearly all adult rats housed in conventional animal facilities. There are no methods available for diagnosis of the condition in the live rat. Gamma globulin determination gives us a method, however nonspecific, upon which a presumption of presence or absence of CRD in the living rat can be based. It is likely

Part A (Cont'd)

that the progress of the disease can be followed by globulin determinations and that this will be useful in further experimentation.

The rise in gamma globulin provides an additional definitive characteristic for a disease which has not been well defined, either pathologically or etiologically.

Proposed Course of Project: Continuation.

Part B included Yes_____ No__X__

Serial No. 4.15
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: PATHOLOGY OF DIROFILARIA IMMITIS INFECTION OF KNOWN INOCULATION DATE AND DOSE IN DOGS

Principal Investigator: Roy Kinard, D.V.M.

Other Investigators: Tom Sawyer, NIAID

Cooperating Units: Animal Hospital Section

Man Years (computed for the 18-month period):
Total: .3
Professional: .1
Other: .2

Project Description:

Objective: To observe the course of experimental D. immitis infection of dogs.

Methods Employed: Known doses of infective larvae from mosquitoes were injected subcutaneously. Ordinary laboratory examinations are performed weekly and postmortem examination, with special dissection of the circulatory system, is performed after natural death.

Major Findings: Most of the dogs, although satisfactorily infected, remain in overt good health with only minor hematological and chemical changes. There has been no opportunity, as yet, to observe postmortem lesions.

Significance: The development of lesions in uncomplicated infections is unknown. Natural infections are of unknown duration and probably caused by multiple inoculations.

Proposed Course of Project: Continuation.

Part B included Yes____ No X

Serial No. 4.16

1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: TRIAL OF PARLETT GEL DIFFUSION TEST FOR TUBERCULOSIS IN RHESUS MONKEYS

Principal Investigator: Roy Kinard, D.V.M.

Other Investigators: Amos Palmer, D.V.M., AHS

Cooperating Units: Animal Hospital Section

Man Years (computed for the 18-month period):

Total:	.2
Professional:	.1
Other:	.1

Project Description:

Objective:	To compare sensitivity and usefulness of the Parlett test to that of the skin test now used.
Methods Employed:	The ordinary tuberculin skin test and the Parlett method in a prepared kit were applied to each animal. Ordinary autopsy was used for confirmation.
Major Findings:	The Parlett test was much less sensitive than the skin test, and, in its present kit form is not useful nor convenient for our purposes.
Significance:	In spite of the alleged usefulness of the Parlett test in man, the tuberculin skin test is confirmed to be the most desirable available method for screening of monkeys.
Proposed Course of Project:	Completed.

Part B included Yes_____ No X

Serial No. 4.17
1. Laboratory Aids Branch
2. Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: FOCAL NECROSIS OF THE LIVER OF RABBITS

Principal Investigator: Thomas D. Moore, Ph.D.

Other Investigators: James R. Ganaway, D.V.M., M.P.H.
Anton M. Allen, D.V.M., Ph.D.
Roy Kinard, D.V.M.

Cooperating Units: Animal Production Section

Man Years (computed for the 18-month period):
Total: .4
Professional: .3
Other: .1

Project Description:

Objective: To attempt the isolation, characterization, and identification of the etiologic agent. To study the pathogenesis of the disease. To recommend measures for control or prevention in the rabbit colonies.

Major Findings: This disease has been recognized only at post mortem examination, and is associated with acute enteritis. The lesions in the liver are indistinguishable from those of Tyzzer's disease of mice. As in Tyzzer's disease, the intracellular bacillus associated with the liver lesions has resisted all isolation attempts. The experimental transmission of the disease has been accomplished with healthy rabbits by means of direct contact with infected rabbits and through exposure of healthy rabbits to soiled bedding from contaminated areas. Success in transmitting the disease by parenteral administration of infected tissues has been meager and unpredictable. The intracellular bacillus, which contains a chain of internal bodies histochemically identifiable as carbohydrate, was found to infect four different types of cells, each of which is noted for its capacity to metabolize and store sugars.

Part A (Cont'd)

Significance: Essential to our knowledge of laboratory animal diseases. This condition has not been described heretofore in rabbits. The microorganism associated with the similar syndrome in mice has not been isolated.

Proposed Course of Project: Continuation.

Part B included Yes_____ No__X__

Serial No. 4.18

1. Laboratory Aids Branch
2. Animal Hospital Section and Comparative Pathology Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: MEASLES (RUBEOLA) IN RHESUS MONKEYS

Principal Investigator: Stephen Potkay, V.M.D.

Other Investigators: James R. Ganaway, D.V.M., M.P.H., CPS
Roy Kinard, D.V.M., CPS
Nancy Rogers, DBS

Cooperating Units: Animal Hospital Section, LAB
Comparative Pathology Section, LAB
Section on General Virology, LVI, DBS

Man Years (computed for the 18-month period):

Total:	.4
Professional:	.25
Other:	.15

Project Description:

Objective: To provide conclusive evidence that the common rash of new Indian rhesus monkeys is measles, and describe the disease.

Methods Employed: Arrangements were made for hemagglutination-inhibition tests for measles antibodies. Ordinary methods for morphological examination of biopsy and postmortem specimens were used.

Major Findings: Clinical observations were those of conjunctivitis, maculopapular skin rash, and varying degrees of facial edema and erythema. Rising HAI titers were usually present. Signs and lesions compatible with those of measles in man were observed.

Significance: This work was obviously essential for the etiological diagnosis of this common disease. Tentative diagnosis based on the typical signs is now possible. The clinical features of the natural occurrence of this disease in simian primates has not been reported previously.

Part A (Cont'd)

Proposed Course of Project:	Completed. A paper is being prepared for publication.
Part B included	Yes_____ No__X__

Serial No. 4.19
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: EVALUATION OF SHIGELLA FLEXNERI (SEROTYPE 4) ATTENUATED VACCINE

Principal Investigator: Amos E. Palmer, D.V.M.

Other Investigators: Samuel Formal, Ph.D., Walter Reed Army Institute of Research

Cooperating Units: Laboratory of Immunology, WRAIR

Man Years (computed for the 18-month period):
Total: .4
Professional: .3
Other: .1

Project Description:

Objective: To attempt the evaluation of an attenuated, non-pathogenic form of Shigella flexneri (4) as an immunogenic agent to immunize rhesus monkeys against this organism while in quarantine.

Methods Employed: The organisms in broth cultures are administered by oral routes either via stomach tube or in the water supply. Animals will be divided into control animals and treated animals and individual records kept on all animals. Stool cultures of all animals showing clinical enteritis will be made at regular intervals.

Major Findings: Project has not progressed enough to evaluate results.

Significance: Shigella flexneri (4) causes an estimated 30% of the enteritis encountered in quarantined primates. The clinical syndrome accredited to this organism is an acute, bloody diarrhea which costs more in treatment, loss of condition, and deaths than any other infectious disease encountered in primates. Any agent which would eliminate this disease would greatly decrease our problems of conditioning animals and increase the quality of animals issued by the Primate Quarantine Unit.

Part A (Cont'd)

Proposed Course of Project:	Continuation.
Part B included	Yes_____ No__X__

Serial No. 4.20
1. Laboratory Aids Branch
2. Animal Hospital Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: EVALUATION OF PROGRAMS FOR IMMUNIZATION OF QUARANTINE DOGS: PILOT STUDY

Principal Investigator: Francis J. Judge, D.V.M.

Other Investigators: Neale D. Stock, D.V.M.

Cooperating Units: Dog Quarantine Unit, AHS

Man Years (computed for the 18-month period):
Total: less than .1
Professional: --
Other: --

Project Description:

Objective: To determine which of three proposed programs is of most value in the prophylactic program for the respiratory disease complex of quarantine dogs.

Methods Employed: Three proposed programs for immunization were used on three groups of dogs with a total of 190 dogs being used. One program called for hyperimmune serum to be injected at the time of acceptance and vaccination in two weeks. The second group received only distemper-hepatitis vaccine upon acceptance and the third group received vaccine upon acceptance and a booster injection in two weeks.

The programs were evaluated by the mortality and morbidity in each group as well as the number of returns after one week in each group.

Major Findings: (1) Commercial hyperimmune serum is not of significant value in the prophylactic program for the respiratory disease complex of quarantine dogs. (2) A second injection of vaccine does not significantly alter the percentage of dogs treated or the percentage of dogs which die in the thirty-day quarantine period. (3) One injection of distemper-hepatitis vaccine at the time of entry appears to be as satisfactory as the other methods evaluated.

Part A (Cont'd)

Significance: Infectious diseases account for high morbidity and mortality in quarantine dogs. Biologic products now used in the program to combat distemper and hepatitis have not been adequately evaluated. It is anticipated that this study will lead to a more effective use of vaccines and antisera.

Proposed Course of Project: Further studies are anticipated that will utilize larger groups of animals and uninoculated controls. Programs to evaluate convalescent serum and canine antibody concentrate are to be carried out.

Part B included Yes_____ No__X__

Serial No. 4.21
1. Laboratory Aids Branch
2. Animal Production Section
3. Bethesda

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: EFFECT OF VARIOUS DAY-LENGTHS ON THE PRODUCTIVITY OF MICE

Principal Investigator: Cobert D. LeMunyan, Ed.D.

Other Investigators: Robert S. Runkle, RFPB, DRS

Cooperating Units: Research Facilities and Planning Branch

Man Years (computed for the 18-month period):
Total: .30
Professional: .05
Other: .25

Project Description:

Objective: To determine whether the length of day (light) has any influence over the reproductive and rearing ability of breeding mice.

Methods Employed: Six cubicles were constructed within a room, each capable of housing fifty pairs of breeding mice. Each cubicle has individual temperature and lighting control. For the purposes of this experiment the temperature and relative humidity will be held constant. The length of day is the variable factor with the various cubicles being set at different day lengths and one control cubicle following the natural lighting cycle. For this phase of the project light intensity will be held constant with a fluorescent source.

Major Findings: This study is currently in the pilot phase with a testing and evaluation of equipment methods and animal heat loads prior to the actual experimental run. The equipment is being checked out, defective materials and equipment are being replaced, and the Caretaker Technician is undergoing training for the final experimental course.

Significance: Animal breeders have long believed that reproductive cycles in rodents are influenced significantly by the length of daylight. However, most of these observations are based on empirical evidence. The very small amount of experimental work which has been done in this field has

Part A (Cont'd)

not concerned itself with laboratory rodents. However, the empirical evidence is strong enough to justify a controlled experimental project such as this one.

The findings of this research will be utilized in the planning of the rodent and rabbit buildings at the NIH Animal Center in Poolesville, Maryland.

Proposed Course of Project: The study of day-length will take one year to complete all phases of the lighting cycle. Following this it is proposed that light intensities and sources be studied and findings again incorporated in the design of the buildings at the NIH Animal Center.

Part B included Yes____ No X

June 1964 January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS 5
Serial Number

2. Computation and Data Processing Branch

3. H. J. Juenemann
Acting Branch Chief

I. SUMMARY

The Computation and Data Processing Branch continued to carry out its principal responsibility of providing centralized computation and data processing services for all of NIH. The Branch's capability was substantially increased by the acquisition of a second Honeywell 800 computer. An important step toward the more fruitful interrelationship of computer technology and biomedical laboratory investigations was taken with the development of a computer training program utilizing an IBM 1620 computer. Mathematicians and programmers of the Branch achieved increasing involvement in important biomedical research projects and surveys. Considerable progress was made in carrying forward a joint NIH/NBS study designed to evaluate and recommend ways of meeting NIH's long-term computing requirements. Of significance for the more immediate future was the development and administrative approval of specifications for a hybrid computing system designed to make computing and analog-to-digital capabilities directly available to laboratory programs.

II. BRANCH PROGRAMS

A. Objective

The basic objective of the Computation and Data Processing Branch is to provide a central computation and data processing service for NIH, using electronic digital computers, electric accounting machinery, oscillogram scanner, plotters, and other data processing equipment. To the extent necessary to foster this objective, the Branch also engages in the development of systems and problem-oriented languages for the more efficient and productive use of Branch resources.

B. Current Programs

The Branch continues to provide a wide range of computation and data processing services in support of biomedical research at NIH. The majority of the program is financed on a fee-for-service arrangement through the NIH Service and Supply Fund. A comparatively modest management fund allocation is used for large capital expenditures and for non-service type operations, such as a computer training program for laboratory scientists.

C. Program Progress and Accomplishments

Of major significance during the reporting period was the acquisition of a second Minneapolis-Honeywell 800 computer which doubled the computing capacity of the Branch. The second computer, as the first, has been manned on a three shift basis, with additional weekend operation when necessary. An IBM 1620 computer was also acquired for use in a training program designed to provide laboratory scientists with the opportunity to fully explore the relationship of their scientific problems to the computer and to assist them in solving some of their problems. The training program has graduated nine classes of approximately 15 students each. The response to the program has been excellent and it has helped to bridge the wide gap between laboratory scientists and the computer sciences.

In response to a growing need for the rapid and versatile conversion of laboratory data from analog to digital form and for closer interrelation between some investigators and the computer, detailed specifications for a hybrid computing system were developed by NIH and have been approved by DHEW. The system, which will be operated on a partnership basis between CDPB and the Laboratory of Clinical Biophysics, NHI, will combine computational and analog-to-digital capabilities.

In cooperation with NIAMD, CDPB accepted engineering responsibility for SPEDAC, a very limited analog to digital converter. Under the arrangement with NIAMD, the device is being used to serve a growing number of laboratory scientists who have problems involving analog data that is automatically captured from experimental situations.

To satisfy the unique data processing needs of the NIH extramural program, two EAM operations were established in the Westwood Building. The primary function of the first unit is to provide extremely fast service to a limited number of users. These users have immediate access to data processing equipment and are thus able to respond quickly to program demands. The second unit provides general data processing services to meet the needs of the various extramural activities located in the Westwood Building. Although both programs have experienced a shortage of operating personnel, they have been successful in accomplishing their objectives.

The first phase of a joint study being conducted by NIH and the National Bureau of Standards to determine the long range computational needs of NIH has been completed and forwarded to NIH management for review.

During the reporting period, the Branch continued to process many recurring programs for the NIH payroll, financial and budget reports, and supply and property records. As a first step in mechanizing the grants management procedures, two new systems were developed in cooperation with the Division of Research Grants and the Financial Management Branch, OD. The first system records the submission of an application for a grant and monitors its progress until it is approved or rejected. The second system is designed to automatically control the payment of approved grants. Both systems are now fully operational.

In the scientific area, a very large number of computations were completed. A few examples are listed.

Analytical tables of the end results of various cancer treatments were completed for presentation at a world wide meeting in Oslo, Norway.

The completion of a large number of analytical programs for the Framingham Heart Study produced a series of tables showing the correlation between the incidence of various types of heart diseases and environmental factors.

The Branch began development of a general purpose "Table Making System" for use in large epidemiological studies. This system, when used in conjunction with other general purpose data handling routines from the CDPB program library, promises good prospects for significantly reducing the programming effort required for the initial analysis of very large data files. The ultimate plan is to make a package of several of these tools which would be directly usable by biometricians. Initial use of the "Table Making System" indicates significant savings of both manhours and computer time.

A series of programs was developed to sequence transfer RNA molecules using overlapping fragments and a logical indexing method. The computer program is part of a large effort to solve the sequencing problem for both proteins and RNA.

An analysis of the relative occurrence of mongolism and leukemia as revealed in cancer data from the 1955 multiple cause of death master file was completed, as was a frequency analysis of the occurrence of selected groups of causes of death. The Branch also completed the Veterans Administration Smoking Survey project, a large-scale epidemiological study involving approximately 250,000 cards, which was requested through NCI for the President's Committee on Smoking and Health.

There was extensive mathematical development in the Branch during the reporting period. Several successful programs were written to analyze infrared spectra of nucleic acids at varying temperatures and to relate them to known spectra, thus enabling the scientist to discover the reaction that takes place in different mixtures as temperature changes. This has led to the development of a new theory on the construction of a nucleic acid molecule.

Extensive development and testing of mathematical models was accomplished in connection with biophysical studies of the physical properties and mechanical behavior of the cardiovascular and pulmonary systems. These biologic systems have multiple degrees of freedom; their mechanical actions are occurring rapidly and are difficult to measure from an instrumentation point of view. Thus the process of validating a mathematical model of the simulated behavior involves extensive comparison with observed data. This places the computer and mathematician in a closed loop that involves formulation of experiment, instrumentation,

capturing and interpreting data, formulation and execution of mathematical models, analysis of computed results and re-formulation of experiment for repeated passes through the loop.

Assistance was rendered to the Clinical Center in automating the analysis of clinical chemistry tests and in establishing various automated systems to automate administrative handling of the processing of the tests, store and retrieve the test results, and subject collected results to statistical analysis. A related information retrieval system was developed to allow inquiries to be made of a file of autopsy results.

Through the efforts of the Branch systems team, augmented by cooperative efforts by Honeywell, the NIH Assembly System (ABACUS) was developed. The system has saved more than 400 hours of computer time in its first three months of use. It has been adopted by several other H-800 installations and has been well received. At the present time an average of 100 Fortran compilations and check-out runs are processed each day, with results being returned to the requestor with an average turn-around time of 2 hours and 22 minutes.

The Branch's library of scientific computer programs has grown to 182. The availability of this store of tested programs permits processing many computational assignments on an overnight basis, with only clerical manhours needed.

D. Problems

With the imposition of a ceiling on Revolving Fund positions, the Branch's staff was virtually frozen for nine months. The situation has now been relieved with an increased allowance; however, the Branch now faces the formidable task of simultaneously training many new employees.

CDPB continues to lose experienced mathematicians and technical personnel to private industry. Although recruiting efforts are directed toward experienced personnel, the Branch usually must resort to hiring young, inexperienced individuals just out of college. After these young people are trained in programming and gain experience, they become vulnerable to the lure of higher salaries being paid by private industry.

E. Program Plans

The Branch is awaiting the conclusion of the joint NIH/NBS study of the equipment configuration which will best satisfy the long range computation needs of NIH. Although the final report is not yet complete, it is evident that a major increase in capacity will soon be necessary. Renovation of the ground floor of Building 12 will begin in early FY'65 to facilitate eventual equipment expansion or modification without undue delay.

F. Publications

Adams, Gordon D., Loren, Allan Z.: Medical and Health Related Sciences Thesaurus. U. S. Dept. of Health, Education and Welfare, Public Health Service Pub. No. 1031, Washington, D.C., Government Printing Office, 1963.

Adams, Gordon D., Loren, Allan Z.: "Complication and Computer Updating of a Medical Sciences Thesaurus," Automation and Scientific Communication. Part 2: 347-348, Oct. 1963.

White, William C., Shapiro, Marvin B., Pratt, Arnold W.: "Linear Programming Applied to Ultraviolet Absorption Spectroscopy," Communications of the ACM, Volume 6, No. 2, Page 66-67, Feb. 1963.

June 1964 January 1, 1963 through June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-6
Serial Number

2. ENVIRONMENTAL SERVICES BRANCH
Branch

3. Edwin M. Lamphere, Sr San E
Branch Chief

I. SUMMARY

As has been the case in past years, the bulk of the Branch workload consisted of short-term investigations and problem-solving in areas of environmental sanitation or engineering. While significant progress is seldom apparent at the termination of any one of these small-scale investigations, considerable progress is apparent at the end of the reporting period.

Besides reviewing all new construction plans for purposes of eliminating future environmental control problems, the Branch is also engaged in the design of some aspects of environmental systems. In conjunction with the Research Facilities Planning Branch, it developed a satisfactory fume hood capable of utilizing 70 percent of nonconditioned air. Use of such a hood in new NIH buildings will make possible considerable savings in heating and air-conditioning costs. While there is nothing new about the concept of using the nonconditioned air, no hoods have been available commercially which would operate satisfactorily under this situation.

The value of planning of environmental systems was shown when Building 10A was placed in operation. The surgical suites' air supply systems, the functional design of which was largely the effort of this Branch, proved to be highly satisfactory. Bacterial counts in the air are about one-quarter of those to be expected in conventional operating rooms.

To improve the hospital sanitation aspect of the Branch program, routine quarterly surveys of all operating rooms were established. In addition, a monthly surveillance program in some of the less critical areas is now under way. These surveys provide an opportunity to spot developing problems and effect control measures before the problems get out of hand.

In further efforts to control infectious organisms, the handling and disposal of infectious wastes have been greatly improved. By working with the Institute and Division individually, the Branch was able to reduce the number of improperly prepared cans of infectious wastes from 50 percent to less than one percent. During the same period, the waste cans labeled as "infectious" have increased by 400 percent. The problem will not be completely solved without a new system. A pilot study of such a system, using paper sacks, is now being conducted in the Clinical Center.

II. BRANCH PROGRAMS

A. Objectives

The objective of the Environmental Services Branch is to insure that a sanitary and otherwise satisfactory environment is maintained at NIH and its field stations.

B. Current Programs

Attainment of the Branch objective is approached through six separate but closely coordinated technical program areas. These are:

1. Institutional environmental engineering which is essentially occupational health engineering adapted specifically to the NIH clinical and laboratory research needs.

2. Hospital sanitation.

3. General sanitation.

4. Insect and rodent control.

5. Development and evaluation of special environment facilities.

6. Bacteriology and chemistry laboratory services.

A sustained effort is made to keep the overall program, as well as individual parts, pointed directly toward the existing and ever-changing needs of the Institutes and Divisions.

Administratively, the Branch approaches its objective by serving as consultant to line management of the Institutes and Divisions. In this capacity, existing or potential environmental control problems are brought to management's attention together with recommendations for practical solutions.

Most of the Branch workload during the period covered by this report has been of the troubleshooting variety where an individual problem is investigated and solved at someone's request. Although this type of activity will always consume a large portion of the staff's time, in recent months it has been possible to make a start on solving basic problems on a reservation-wide basis rather than on the basis of a series of isolated small problems. For example, the problem of improper handling of infectious wastes was approached on a reservation-wide scale rather than as constantly recurring individual problems.

With regard to the technical program areas, institutional environmental engineering is primarily concerned with problems involving air pollution; toxic and noxious fumes; odors; dust; sound; vibration; water, both tap and high quality; illumination; waste disposal; engineering aspects of decontamination and sterilization; ventilation; etc.

The hospital sanitation activities are concerned only with the patient care areas of Building 10. They are aimed primarily at infection control, but also include general sanitation work. Routine surveillance is carried out in the operating rooms, nursing units, and the various departments such as X-ray, Outpatient, Dental, etc. While the majority of the workload is concentrated on the surveillance measures necessary to keep infections from occurring, locating the source of infections which have occurred occupy a considerable amount of time.

General sanitation activities are carried out throughout the NIH reservation and in rented facilities in nearby areas. Emphasis is placed on surveillance of infectious waste disposal, animal rooms, cafeterias, snack bars, vending machines, and housekeeping practices.

Closely associated with the general sanitation program are the insect and rodent control activities. In order to prevent undesirable infestation and the resulting potential for cross infection between animals, patients, and staff members, an active control program is pursued. This consists of routine insecticidal application and maintenance of rodent traps and poison bait stations, together with evaluation of factors which encourage the presence and reproduction of insects and rodents. All insecticides are screened for gross hormonal activity.

Development and evaluation of special environmental equipment activities are performed as a service to the research scientist who requires something out of the ordinary in a research environment. Work usually takes the form of preparation of functional designs for those items of equipment not available commercially. All work is tailored to the needs of the interested scientist. Examples of such unusual environments include germfree, virus-confining, anaerobic, and trace element-free. This aspect of the Branch program has at least temporarily been deemphasized in order to place additional emphasis on institutional environmental engineering.

Bacteriology and chemistry laboratory services are organized primarily to provide the necessary support for the environmental sanitation and engineering programs. However, to the maximum extent possible, these services are made available to anyone in the Institutes or Divisions who may request them. All bacteriological monitoring of the central SPF animal production colonies is carried out by the Environmental Services Branch laboratories.

C. Program Progress and Accomplishments

As has been noted previously, the bulk of the Branch workload consisted of short-term investigations and problem solving in areas of environmental sanitation or engineering. No attempt will be made to report in detail on this aspect of the program, but several examples are as follows:

a. Complaints were received and investigated at a rate of more than once weekly on odors, noise, temperature and humidity, dust, fumes and toxic gases, and illumination in the above order of frequency. Solutions ranged from merely removing a dead mouse from the partitions to the installation of extensive exhaust and fume hood facilities. Trouble calls of this type

rarely require less than one man day in time, and may often take two man weeks or more depending on the complexity of the problem.

b. All items of environmental health significance in Building 10A were checked before it was placed in operation. This included a detailed sanitary survey of the whole building, adjustment of the ventilation systems in the operating suites, measurement of bacterial quality of the air entering the operating suites, and determining the vibration levels in all parts of the structure.

c. In connection with NIH new construction program, all plans were carefully reviewed for the purpose of eliminating future environmental control problems.

d. A steam formaldehyde decontamination procedure was developed for laboratories, animal rooms, vehicles, etc. Under most circumstances this is as satisfactory as beta propiolactone decontamination, and much less hazardous and time-consuming.

e. Deterioration of the quality of tap water delivered to NIH resulted in the need for developing a variety of water treatment facilities, descaling procedures, filters, and similar corrective measures.

f. A problem of contamination of the surface of blood containers which are taken into the operating rooms was traced back to the supplier. DBS is now conducting a routine sanitary inspection of facilities supplying blood to NIH.

g. Continual sanitary surveillance was carried out in the patient related areas of Building 10. All NIH or contract food service facilities were inspected on a routine basis. All animal rooms were routinely inspected for conditions of sanitary significance.

In the past the Branch carried a considerable load of routine service activities. In order to concentrate on the major objective, most of these service activities have been given to someone else. Some routine service work remains and examples are as follows:

a. The quality of distilled water produced by all central systems and a number of local stills is monitored on a daily or weekly schedule. Quarterly determinations specifically for copper content are made.

b. In connection with Institute purchases of laboratory stills, autoclaves, isolators, and similar equipment, specifications are prepared; requisitions are checked against requirements; and trips for factory inspections are made.

c. Chlorination of new water lines, repaired water lines, cooling towers, etc., are either carried out or supervised.

d. Insecticiding is routinely carried out in all NIH buildings on a six-week schedule. Wild or escaped rodents in Building 10 are trapped and poisoned elsewhere.

Significant progress or accomplishments in this Branch are seldom apparent at the termination of some small-scale investigation or routine survey.

They are a result of continued effort in the more routine areas, or the result of a major study designed to solve some major problem. The following paragraphs describe some of the more important progress and accomplishments within this reporting period.

Infectious waste handling and disposal are always a problem in a biomedical research institution. By working with each Institute and Division individually, the number of improperly handled infectious waste cans has dropped from 50 percent to less than 1 percent. In addition, the number of cans marked "infectious" by the research laboratory has increased by 400 percent, while the total number of waste cans has increased by only 10 percent. While this is a considerable improvement, the problem is not yet solved. Solution will require a different system. Such a new system using paper sacks instead of metal cans is now being tried on the 10th floor of Building 10. Results to date are very promising.

A problem of significance to most researchers who use animals is the quality of the animal feed. Provision has been made for all NIH animal feed contracts to include specifications covering the sanitation aspects of feed preparation. Before a feed contract is let, the plant is inspected by a qualified sanitarian to be sure the feed will not be contaminated by bird or rodent droppings, chemicals, or hormone residues.

Prevention of infection or communicable disease problems in the Clinical Center is the primary goal of the hospital sanitation aspect of the Branch program. A routine quarterly survey of all operating rooms was established and a monthly surveillance program in some of the less critical areas is now under way. Despite the surveillance program, problems do occur, and some of the worst result from organisms other than Staph aureus. Of the three major problems of this type which have occurred during this reporting period, the Environmental Services Branch located the source of two. Another item of significance in the hospital sanitation area was the development of a tool for objectively measuring the dirt on floors or other surfaces. This tool is now being manufactured commercially.

While the highly satisfactory performance of the air supply system in the operating suites of Building 10A cannot be attributed to much that was accomplished in this reporting period or by staff members currently assigned to the Branch, the fact remains that the functional design was largely the effort of the Environmental Services Branch. Bacterial counts in the air of the new operating suites are about one-quarter of those to be expected in a conventional operating suite.

In laboratories where any toxic or noxious fumes are generated, good fume hood performance is essential. Heretofore, the only fume hood which could be expected to give first-rate performance was designed on the basis of having sufficient room air available to provide the necessary velocity through the face of the hood. This is very expensive, since all room air must be heated or cooled. In conjunction with the Research Facilities Planning Branch, a fume hood was developed for the new NCI and NIMH/NINDB Buildings which will perform satisfactorily when using 70 percent nonheated or cooled air and only 30 percent room air.

As noted previously, surveillance of distilled water quality is a responsibility of this Branch. Overall, the quality of distilled water at NIH has improved considerably over the past 18 months. It is not possible in a report of this type to delineate precisely the amount of improvement, but as a rough indication the average of all specific resistance measurements shown on the January 7, 1963 distilled water report was 629,565 ohm-cm; the average of all specific resistance measurements shown on the April 29, 1964 report was 948,800 ohm-cm.

D. Problems

The major current and foreseeable problems stem from an inability to arrange transfers of commissioned personnel in the Full and Senior grades to the Environmental Services Branch from other PHS Divisions. Commissioned personnel are mentioned specifically because the Corps is the only pool of well-trained manpower in the job categories of interest to this Branch. Personnel recruited elsewhere can be trained, but the process is very time-consuming. Amounts of training time range from a few months for personnel recruited from state health departments to years for those recruited from industry. While technically qualified personnel can be found outside the Corps, lack of appreciation for the essential administrative aspects of an environmental health program throws such an additional load on the supervisory staff that a bottleneck results.

At the present time, the Branch could not turn out any more or better work if the number of staff members in grades GS-7 through 9 or Jr. Asst. through S. A. were tripled.

Staff turnover, whether commissioned or civil service, appears to be a fact of life, and the minimal on-the-job training required for the middle commissioned grades is a distinct advantage.

Constant on-the-job training for Branch personnel and constant agitation for a better transfer system within the PHS appear to be the only solution.

E. Program Plans

Basic objectives of the Branch will not change in the foreseeable future. However, recent and anticipated developments necessitate some shifting of emphasis within the Branch.

Most recent thinking in the field of hospital infection control indicates that for effective control of the environment, attention must be directed to dozens of small details. Primary attention given to only a few of the major considerations has proven to be inadequate. This means that more routine monitoring than has been thought satisfactory in the past is needed even if there were to be no changes in the clinical research program. However, none of the research programs are static, and it is anticipated that work will be carried out on surgical procedures more drastic than at the present time.

It is expected that progress in some of the laboratory research programs will result in finding a chemical or biological agent which causes one of the chronic diseases in humans. Adequate environmental control techniques must

be worked out prior to that time to allow the research effort to move forward without undue hazard to the scientific staff. In fact, the necessary techniques and surveillance measures are needed at the present time. The first step will be the establishment of a routine fume hood surveillance program. Every hood on the reservation will be labeled as to its suitability for use with hazardous materials.

In line with these current and anticipated needs, the "hospital sanitation" and "institutional environmental engineering" aspects of the Branch program will be emphasized at the expense of other programs, particularly "development of special environment facilities."

With the completion of the new NCI and NIMH/NINDB Buildings plus NIH Animal Center, insect control problems may or may not exceed the capabilities of the present staff. Experience has shown that insect infestation problems will occur in the NIH buildings when routine insecticide applications are scheduled at 19 week intervals. The problems are minimal when the applications are scheduled at 6 week intervals. Before requesting additional personnel, it is planned to see what happens at some intermediate schedule.

The Branch, as presently organized, could not cope indefinitely with the heavy present schedule of plan reviews for new construction and major improvements. This phase of the workload is expected to diminish greatly within the next few months, and no reorganizing or emphasis shifts appear to be in order.

F. Publications

1. Cox, James M., and Boettcher, Richard A., "Sanitation Prerequisites in the Production and Storage of Laboratory Animal Feeds." Laboratory Animal Care, vol. 13, No. 5. October 1963.

2. Weatherby, Robert J., and Furfari, Santo A., "Why Measure Floor Dirt." Journal of Environmental Health, vol. 26, No. 4. January-February 1964.

3. Herman, Lloyd G., and Fournelle, Harold J., "Flavobacteria: A Water-borne Potential Pathogen." To be published in Chemotherapia.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-7
Serial Number

2. RESEARCH FACILITIES PLANNING BRANCH

3. H. M. Biggs
Branch Chief

I. SUMMARY

During the past 18 months, the Research Facilities Planning Branch program of coordinating the planning and construction of new facilities has increased in volume. Day-to-day working relationships have been improved between NIH and PBS representatives but still somewhat less than satisfactory. Region III, GSA, has assigned to NIH a competent Project Manager with full responsibility to properly supervise construction on all NIH projects. New working relations have been established with WSSC in connection with the extension of NIH master utilities.

Engineers related to the design program of the Branch have been engaged on more than 15 major projects totalling $67,843,000 in design and construction costs. Further support of the NIH design and construction programs has been accomplished through the development of design guidelines, criteria and standards in such areas as animal caging, floor and wall coverings, laboratory equipment, etc.

One major construction project was started during 1963, namely, the NIH Animal Center, Phase I. This project includes a farm animal building and a kennel building for the holding and quarantine of animals for research. Two residences, a central power plant, and utilities are also included at a total cost of $3,577,500. The surgical wing of the Clinical Center was completed and occupied during 1963.

II. BRANCH PROGRAMS

A. Objectives

The major objective of this Branch is the coordination of the planning and construction of new facilities on the NIH Reservation, Bethesda, and at its field stations. This is supplemented with a secondary objective of providing development engineering services and technical assistance where special problems in design or construction are encountered.

B. Current Programs

The design program is primarily responsible for determining that new construction provides for the program needs of NIH research scientists. A

staff of professional engineers is employed to render limited consulting service and to provide coordination between contract architects, Public Buildings Service liaison architects, NIH research staff members for whom facilities are being provided, and other branches of the Division of Research Services.

The construction program provides a close technical control of new facilities for NIH during the construction phases. A staff of construction management engineers maintains surveillance during the process of construction to determine that the facility is constructed according to plans and specifications, with particular emphasis on surveillance of construction and equipment peculiar to NIH requirements.

The current development program is directed toward improving the functional aspects of facilities presently under design as well as contributing standards, recommendations, and solutions to operational problems encountered in existing NIH facilities. Technical support rendered to the health research facility design and construction program falls into a wide spectrum of activities, such as: (a) planning of areas to accommodate special research techniques; (b) development of equipment peculiar to laboratory processes and personnel safety; (c) improved care and quality of research animals through automation and environmental control; (d) standardization of laboratory furniture to effect economical procurement measures; and (e) search for improved materials to reduce maintenance and operation costs. To facilitate this technical support, a reference library is maintained for engineers in the Branch and contains engineering reference material directly concerned with the design and construction of new facilities.

C. Progress and Accomplishments - Design Program (for a summary of all design projects, see Table I, page 7-13)

NIMH/NINDB Building (Building 36)

Design of this project was started in July 1961. The preliminary design had been approved earlier in 1962. Tentative sketches for this project were submitted for approval November 7, 1962. In March 1963, the A/E forwarded a request for $42,000 fee adjustment to PBS to cover changes in the tentative sketches for both NCI and NIMH/NINDB buildings which, reportedly, were outside of the scope of his contract. This request was finally approved by the GSA Administrator on May 28, 1963, and the A/E returned to work on the tentative design stage resubmission on May 31, 1963. The revised drawings were submitted by the A/E on August 22, 1963, and final approval of the tentative design drawings by PBS was given on September 13, 1963.

Approximately six weeks delay resulted from the refusal of the A/E to proceed into intermediate working drawings until the location of the air intakes in the NCI Building had been resolved. This was finally settled on October 23, 1963, when PBS reluctantly concurred in our acceptance of the air intakes at the loading dock area.

The intermediate working drawing submission was received on March 20, 1964. Completion of the working drawings and specifications is scheduled for June 1964. The PBS estimate of cost at the intermediate submission indicates that the base bid (cost of building without alternates) is well within the available funds. If the present design schedule is maintained, construction for this project will be started early in 1965.

NCI Building (Building 37)

This project is being designed concurrently with the NIMH/NINDB Building by the same A/E firm, and it follows the same schedule. The lowest cost estimate of $8,280,000 was in excess of the available funds, and revisions in design were required to reduce the cost of the project.

The A/E's request for a fee adjustment of $42,000 for both NCI-NIMH/NINDB buildings in March 1963, based on his claim that many recommendations on the tentative sketches were outside the scope of his contract, caused considerable delay in design. The fee adjustment was approved by the GSA Administrator on May 28, 1963, and the A/E started work on the tentative design resubmission on May 31, 1963. The revised drawings were submitted on August 22, 1963, and final approval by PBS was given on September 13, 1963.

The intermediate working drawings were not started by the A/E until October 23, 1963, after resolution of the location of the air intakes. The intermediate working drawings were received in March 1964, and the complete working drawings are anticipated in June 1964.

If the present design schedule is maintained, construction for this project will be started early in 1965.

NCI-NIMH/NINDB Cafeteria (Building 35)

Approval was received in May 1963 to proceed with the design of the Cafeteria Building, which had been deferred since August 1962. Due to a considerable delay by the A/E in his schedule for presenting the design concept of the building, diagrammatic sketches were not received until November 12, 1963.

The A/E's concept of the Cafeteria, including the private seating area for 102 scientists, was approved on February 7, 1964, by the RFAC. This approved concept included certain modifications in order that the project would be within the budgetary allowance.

The exterior design of the Cafeteria was approved by the RFAC on April 8, 1964. The tentative stage submission was received on April 27, 1964, and the intermediate working drawings are anticipated in June 1964.

The schedule calls for submission of complete working drawings in July 1964 while the complete working drawings for Buildings 36 and 37 are being reviewed.

NIH Animal Center, Phase I

Design of this project was completed in January 1963. The construction contract was awarded and construction began in June 1963. Construction work has pro-

gressed approximately on schedule, and completion is scheduled for December 1964.

NIH Animal Center, Phase IA

The BOB set a limit of $1,330,000 total cost for construction of the project as opposed to the $1,735,500 requested in the original POR. NIH revised the POR in June 1963 to conform to the budget limitations, and planning funds were apportioned by the BOB. The reduced program included a General Laboratory Building, an Animal Behavior Laboratory, and a waterfowl habitat for NIMH. Also included was a Primate Building for Laboratory Aids Branch, an incinerator, and supporting utilities and grounds for all Phase IA buildings. Diagrammatic drawings were submitted to NIH on January 17, 1964. Revised diagrammatic drawings were required to meet the needs of the program. The revised drawings were submitted March 19, 1964. Design completion is expected in December 1964.

NIH Animal Center, Phase II

During 1963 initial steps were taken in the preparation of the POR for the Agricultural Management Building, Small Animal Production Facilities, Waste Chemical Disposal Facility, Third Kennel Wing, Cages for Primate Building, a third residence, and supporting utilities and grounds work. Deleted from Phase II and placed in Phase III were: The Records Storage Building, Dormitory, and the Animal Virus Isolation Facility (NIAID). The Hazardous Building (NCI) was entirely deleted from the Phase II program. Design work is expected to begin in October 1964 for Phase II.

NIH Office Building Extension

Planning funds in the amount of $700,000 were provided for this project in FY 1962. An amount of $5,500,000 for construction is included in the FY 1965 appropriation request. Pending resolution of the means by which vehicle parking facilities would be provided, the BOB approval of the POR was delayed until May 1963. The POR, as approved by the BOB, provided for a facility not to exceed 230,000 gross square feet at a total cost for design and construction of $6,200,000, and with provisions for "on-grade" vehicle parking. The design contract with the A/E was negotiated in July 1963. A number of preliminary studies and design schemes were prepared by the A/E and reviewed by PBS and NIH, and formal diagrammatic sketches were submitted in March 1964. Tentative drawings are scheduled for submission in June 1964. The design is scheduled to be completed in January 1965 and construction in August 1966.

Master Utilities Extension

Planning funds for the extension to the utilities systems were provided in FY 1962, and $4,850,000 was appropriated in FY 1963 for construction costs. An A/E firm completed a master site plan study and report in December 1962, and the POR for the extension to the NIH Utilities Systems was completed in December 1962. This porgram consists of two phases. Phase I includes the utilities required to support the current construction program consisting of the Cancer Research Building; NCI Cafeteria; the NIMH/NINDB Building; the Biologics Standards Building Extension; the NIH Office Building Extension; the fourth extension to the Air Conditioning Plant; the Central Services

Building #12 Extension; the renovation of the old Cancer Building #6, and the corrections of deficiencies in existing utilities systems. This first phase will cost an estimated $5,144,600, including planning and construction.

Phase II of the Master Utilities Extension program provides those utilities required to serve the remaining buildings scheduled in the NIH Master Plot Plan. The cost of this work is estimated to be $4,514,400.

One portion of Phase I of the MUE (which includes Buildings 29A and 12A) has progressed to the final working drawing stage during April 1964 and is expected to be completed during May 1964. The final working drawings for the remainder of the work under Phase I are expected to be completed in August 1964.

The new buildings under construction and presently under design will require an increase in water and sewer service to the NIH Reservation. Representatives of NIH and GSA have met with the Washington Suburban Sanitary Commission (WSSC) to discuss this increased service; however, these negotiations have been proceeding slowly. Separate contracts with WSSC are being negotiated by GSA for construction of new water mains, for sewer service, and for water consumption.

Gerontology Building

The POR for this project was completed in March 1962. Delays were encountered in completing the collaborative gerontology program with Baltimore City Hospitals, and in the final transfer of land to the U. S. Government. The A/E was selected early in 1963, and an A/E contract was negotiated by GSA on May 1, 1963. The Notice-to-Proceed with the design was issued on May 27, 1963. Diagrammatic sketches were submitted on August 19, 1963, and after extensive restudies, were approved on December 27, 1963. Tentative sketches were submitted on April 3, 1964. The review was completed April 30, 1964. Plans and specifications are scheduled to be complete in February 1965, and beneficial occupancy of the facility is expected about June 1967.

Division of Biologics Standards Extension

Planning funds of $200,000 were allocated in FY 1962 and supplemented with an appropriation of $150,000 in FY 1963 to plan this facility. Construction funds of $4,300,000 were provided in the 1964 appropriation.

The POR was completed in March 1962 and, after FY 1963 funds became available, the design contract was negotiated in October 1962. The diagrammatic drawings were submitted January 15, 1963, and were approved February 8, 1963. Notice-to-Proceed into the tentative design phase was issued February 22, 1963. Tentative sketches were submitted June 3, 1963, with Notice-to-Proceed into intermediate working drawings being issued to the A/E on August 6, 1963. Intermediate working drawings were submitted on November 1, 1963, and were approved December 17, 1963. The submission of complete working drawings, originally scheduled for January 15, 1963, was delayed four months to May 15, 1963, by negotiations over an amendment to the A/E contract. The design is scheduled to be complete in July 1964. Beneficial occupancy of this structure is scheduled for March 1966.

NINDB Perinatal Research Laboratory, San Juan, Puerto Rico

An appropriation of $600,000 for design and construction was provided for this project in FY 1963. The DHEW and the BOB, during 1962, agreed to supplement the original appropriation with an additional $250,000. Extensive modifications to the POR and the necessary legal and transfer actions delayed submission of the POR to the BOB. The POR was forwarded to the BOB, through PHS, in March 1964. The POR provides for a facility of 26,000 gross square feet at a total cost of $850,000. Formal transfer of the land to the United States Government by the Puerto Rico Medical Center Board of Directors is anticipated in June 1964. It is expected that the design contract can also be negotiated in June 1964. Design is scheduled for completion in June 1965, with beneficial occupancy of the building in August 1966.

Basic Research Laboratory, Lexington, Kentucky

Funds amounting to $350,000 were appropriated for design and construction for this project in FY 1961. The project was designed by an architect under contract to GSA and placed on the market for bids in June 1962. The cost estimate, prepared with the completed working drawings, exceeded available funds by approximately $50,000. An additional $50,000 was apportioned by the BOB. However, the lowest bid received was approximately $80,000 above the total available funds. The project research program was reviewed by the NIMH, and a new POR was prepared in the Fall of 1962. A new cost estimate was prepared with the cooperation of PBS, and at the end of 1962 arrangements were made to negotiate another design contract based on a POR providing approximately $320,000 for the construction and a gross area of 12,000 square feet. In April 1963 the A/E contract was negotiated. The diagrammatic drawings were submitted on May 21, 1963, and were approved. Notice-to-Proceed into tentative drawings was issued June 13, 1963. Tentative sketches were submitted on July 29, 1963, with Notice-to-Proceed with intermediate working drawings being given on August 14, 1963. The intermediate working drawings were submitted September 28, 1963, and were approved November 3, 1963. On December 7, 1963, complete working drawings were submitted. The cost estimates exceeded available funds at this stage, and the project was delayed pending a determination of the availability of additional funds to cover the deficit. The A/E was given the notice to complete final working drawings on January 27, 1964, but PBS requested resubmittal of mechanical drawings. The final working drawings were submitted partially on March 10, 1964, with the remainder on March 29, 1964. Construction is scheduled for completion by August 1965.

Clinical Center Cafeteria Extension

On May 17, 1963, the FY 1964 budget estimate of $695,000 was submitted by DRS. Congress appropriated funds in October 1963. The POR was approved by the Director, NIH, on April 3, 1964, and submitted to the BOB via PHS and DHEW for approval and apportionment of planning funds. DRS was informed on February 3, 1964, that NIH had been granted authority for direct negotiation and administration of the design and construction contracts. Upon approval of the POR, PEB will assume responsibility for the coordination of the design and construction of this project. The award of the A/E contract and commence-

ment of the design is scheduled for July 1964, with beneficial occupancy of the facility expected approximately December 1966.

NIH Library Relocation

On May 17, 1963, the FY 1964 budget estimate of $900,000 was submitted by DRS. Congress appropriated funds for the project in October 1963. The POR was approved by the Director, NIH, on December 24, 1963, and submitted to the BOB via PHS and DHEW on January 31, 1964, for approval and apportionment of planning funds. On February 3, 1964, DRS was informed that NIH had been granted authority for direct negotiations and administration of the design and construction contracts. Upon approval of the POR, PEB will assume responsibility for the coordination of the design and construction of this project. The award of an A/E contract and commencement of the design is scheduled for June 1964, with beneficial occupancy of the facility expected in November 1966.

Warehouse Extension

The FY 1964 appropriation included $780,000 for planning and construction of additional warehouse space on a proposed fourth floor to Building 13 on the NIH Reservation. An intensive study of the proposal has indicated that a fourth floor addition is not the best solution from the standpoint of efficient warehousing operations. An alternate solution, which would provide a separate structure, was submitted to and approved by the PHS Division of Finance and Division of Administrative Services in February 1964. This warehouse building would be located within the general service area of the NIH Reservation and would encompass 43,000 gross square feet of floor space, the same floor area as originally proposed. Planning and construction costs will not exceed $780,000. A POR for the alternate facility is scheduled for completion in May 1964. It is expected that the design contract can be negotiated by September 1964. Scheduled completion of design is August 1965 and completion of construction in January 1967.

Progress and Accomplishments - Construction Program (for a summary of construction projects, see Table II, page 7-15)

The following projects were placed in operation during 1963: (1) Surgical Wing, Building 10-A Instrumentation; (2) NLM MEDLARS; (3) NLM Roads and Sidewalks. Construction was completed quite close to the estimated time schedules and did not adversely affect program activity schedules. There was limited delay in making some of the final corrections. Most of this delay can be attributed to the highly complicated nature of each correction which required considerable technical guidance.

The contract for construction of the first phase of the NIH Animal Center at Poolesville, Maryland, was awarded in June 1963. Award of the contract had been delayed slightly due to the receipt of competitive bids somewhat higher than the estimate. Higher bidding was probably due to several factors, but primarily to the remoteness of the site. Construction progress has been satisfactory, generally, in spite of poor construction weather throughout the winter. Nearly all of the underground utility systems have been completed,

and progress is good on the other construction aspects of the project.

In the past, the overrun of construction time schedules has, in some instances, had adverse effect on the NIH biomedical research program. With this in mind, considerable time has been spent and evaluation given toward methods of improving the contract administration which has contributed to the delays. Some progress has been made in this area through the permanent assignment to NIH of a PBS Project Manager with full supervisory control over PBS field personnel and a greater latitude of authority. Improvements for better streamlining of operations between NIH, PBS, and the Contractor have been implemented. Toward this end, RFPB has prepared and distributed two pamphlets: "Administrative Guidelines for the Construction of New NIH Facilities" and "Standard Operating Procedures - Construction Section."

Progress and Accomplishments - Development Program

Reports of program studies are normally distributed to interested NIH organizations. However, requests from extramural sources, which usually originate from the Division of Research Facilities and Resources, are also honored. Considerable support to the program (on an as-needed basis) has been provided by contractual means. This technique improved both the quality and quantity of program accomplishments through efficient use of both manpower and finances.

1. Collaborative Projects

   a. Improving Animal Care Facilities (in collaboration with Laboratory Aids Branch, DRS).

      Because laboratory animal care facilities are vitally important to NIH, a continuous project was previously undertaken by the Laboratory Aids Branch and the Research Facilities Planning Branch to conduct research and development promoting improvements in animal care facilities. Work currently underway in this project includes: (a) assistance in the preparation of the POR for the small animal production facilities for new NIH projects; (b) mechanization of animal care processes, especially in the areas of cleaning and watering; (c) new designs for cages for the NIH Animal Center, incorporating the principles of mechanization and improved fabrication techniques; and (d) study of photoperiodism in mice.

   b. NIH designed Fume Hood (in collaboration with Environmental Services Branch, DRS).

      In recognition of the need for a fume hood of improved operational and safety aspects for NIH applications, the testing and design of a prototype model embodying certain aerodynamic virtues and principles was undertaken collectively by Environmental Services Branch and

Research Facilities Planning Branch. Participation by RFPB in the project, which will provide an auxiliary air fume hood design for NCI-NIMH/NINDB Buildings and possibly future NIH facilities, has been mainly as project coordinator.

2. Miscellaneous Services

In addition to the direct support rendered to the NIH design and construction program through engineering studies, service of a cooperative nature applicable to establishment of new design standards for animal care equipment, as well as design guidelines and criteria for animal facilities, was supplied to various groups. These groups included Procurement Section, SMB, National Heart Institute, National Cancer Institute, and the Veterans Administration.

As a means of stimulating new approaches and introducing new concepts, the staff has made numerous visits to both laboratory and animal facilities. Information from private institutions as well as other government facilities has served to foster novel ideas and solutions to operational, design, and construction problems.

To support the facilities design and construction program, the staff periodically reviews plans and specifications to insure that the design is compatible with program requirements and represents not only a sound architectural solution but also a good functional solution.

In recognition of the valuable information disseminated by means of seminars and lectures, a member of the Section staff has taken an active part in organization and development of a DRS-sponsored engineering lecture series designed to further the exchange of information on topics of interest to facilities personnel in local government agencies.

Early in 1964 the Section sponsored a seminar concentrating on fume hood design and operation. Participants included NIH scientists and engineering groups and a representative of a well-known fume hood manufacturer.

Members of the Section participated in an orientation program for Chief Engineers from PHS National Regional Offices.

3. Informational Reports (exclusive of those published in technical journals)

   a. Criteria For Constant Temperature Rooms in Connection with NCI-NIMH/NINDB Buildings

b. Improved Vibration Standards for Electron Microscope Operation

c. Planning Glassware Washing Areas (draft)

d. Incinerator Design Criteria

e. Low Temperature Refrigeration Study

f. Laboratory Benchtop and Sink Material Test Report

g. Epoxy Flooring Materials (interim)

h. Distilled Water Distribution Systems

i. Laboratory Casework Standards (draft)

j. R&D Team Project Reports

D. Problems - Design Program

NIH is continually confronted with loss of time in obtaining approvals and clearances during the different stages of design. Much of this time is lost in review stages. In negotiating A/E contracts, a time schedule is mutually agreed upon between the Government and the A/E. This schedule includes periods for review. Invariably, it has been our experience that the review periods are considerably longer than those included in the A/E contract. Part of the problem is that the review periods are unrealistically short; another is the lack of sufficient personnel at PBS in certain disciplines to perform the review.

Efforts have been made to accelerate the review periods at NIH and at the PBS level. RFPB Project Engineers are now required to maintain close supervision of the design schedules which are a part of the A/E contract. The engineers regularly prod the A/E directly or through PBS to maintain individual projects on schedule. Experience has shown that "on-the-board" reviews in the offices of the A/E have been most effective in accelerating design reviews. In March 1964 the Public Buildings Service recognized that their backlog of design reviews was increasing and issued instructions to their personnel which would accelerate its review periods. It is not known whether this will be for a limited time or will be the policy of PBS. NIH did receive prompt review by PBS of the tentative stage drawings for the Gerontology Building. Other projects which seemed to have benefited from the accelerated procedure are the National Cancer Institute/National Institute of Neurological Diseases and Blindness & National Institute of Mental Health Buildings at the intermediate review stage. One other continuing corrective measure which NIH pursues is that in which the Chief, DRS, periodically reviews the NIH program with the Assistant Commissioner for Design and Construction, PBS. These contacts have been fruitful in specific instances. However, it appears that there is limited authority for decision at the PBS working level.

Problems - Construction Program

The Public Buildings Service, which has direct responsibility for construction contract administration, has encountered increasing difficulty in hiring and retaining competent personnel for construction supervision and inspection. In an effort to overcome this lack of personnel, our most recent contracts with Architect-Engineer firms have included provisions for supervision of the construction by the A/E at the option of the U. S. Government.

Several areas of improvement in the preparation of specifications are needed to assist the Project Manager to better control the construction time schedule. These are areas in which it is planned to participate with PBS to our mutual advantage.

E. Program Plans - Construction

During the next three years the volume of the NIH construction program is to be greatly increased. The needs for technical program surveillance will increase proportionately. Staffing with qualified and experienced personnel to meet these needs will be of high priority.

Program Plans - Development

The current development program emphasizes strongly the design support function for the NIH facilities planning, design, and construction program. Significant areas of investigation* presently under study are as follows:

1. Laboratory Casework Standards
2. Development of Partition Criteria
3. Heat Exchanger Applications
4. Cold Room Study
5. Resistant Flooring Materials
6. Planning Cage and Glassware Washing Facilities (ESB)
7. Caging for NIH Animal Center (LAB)

* Collaborating organization shown in parenthesis

F. Publication and Patents

A. Publications

1. Planning the Electron Microscopy Suite, American Institute of Architects Journal Vol. 39 (5)
2. Planning the Electron Microscopy Suite, Laboratory Management Vol. 2 (1)

3. Laboratory Animal Housing, Laboratory Management, Vol. 2 (1)

4. Laboratory Animal Housing, Part I, American Institute of Architects Journal Vol. 40 (3)

5. Laboratory Animal Housing, Part II, American Institute of Architects Journal Vol. 40 (4)

6. Waste Piping Study, Plant Engineering, Vol. 18 (4)

TABLE I- RFPB - 1963 Program of Authorized Design Projects

Project	Design Completion Date	Construction Completion Date	Construction Cost*	Planning Cost	Total Project Cost	A/E Designer
NIMH/NINDB Bldg.	8/64	6/67	$8,620,000	$ 619,000	$9,239,000	SH & GA, Inc.**
Cancer Research Bldg.	8/64	6/67	8,886,000	610,000	9,496,000	SH & GA, Inc.
NCI-NIMH/NINDB Cafeteria Bldg.	8/64	6/67	749,000	51,000	800,000	SH & GA, Inc.
NIH Animal Center, Phase I	1/63	12/64	3,342,000	201,000	3,543,000	HSM&M**
NIH Animal Center, Phase IA	11/64	3/66	1,235,000	95,000	1,330,000	Heery & Heery
NIH Animal Center, Phase II & III	11/65	9/67	8,331,000	578,000	8,909,000	Not available
NIH Office Bldg. Ext.	1/65	8/66	5,850,000	350,000	6,200,000	K, L, & C** C, G, & Van A.
NIH Master Utilities Ext. Phase I	11/64	3/67	4,784,600	360,000	5,144,600	HDNA**
Phase II	N/A	N/A	4,199,400	315,000	4,514,400	Not available
Gerontology Bldg.	2/65	7/67	7,500,000	1,000,000	8,500,000	CS & D & LW, C & W**
Bldg. 12 Ext.	1/64	6/65	1,449,465	80,197	1,529,662	JE, C & K**
Bldg. 29-A, DBS	7/64	5/66	4,300,000	350,000	4,650,000	SH & GA, Inc.
Puerto Rico Perinatal Lab.	6/65	8/66	790,000	60,000	850,000	Not available

TABLE I (con't) - RFPB - 1963 Program of Authorized Design Projects

Project	Design Completion Date	Construction Completion Date	Construction Cost*	Planning Cost	Total Project Cost	A/E Designer
Basic Research Lab. Lexington, Ky.	4/64	6/65	$ 348,000	$ 37,200	$ 374,000	Lawrence Cammack Lexington, Ky.
Library Reloc.	6/65	12/66	831,000	69,000	900,000	None
Clinical C. Cafe. Ext.	7/65	12/66	658,300	36,700	695,000	None
Warehouse Extension	8/65	11/67	723,500	56,500	780,000	Not available
					$67,843,000	

* Includes construction contract cost and other construction cost

**

SH & GA, Inc. - Smith, Hinchman & Grylls, Associates, Inc.

HSM&M - Hayes, Seay, Mattern & Mattern

K, L, & C - Keyes, Lethbridge & Condon
C, G & Van A. - Carroll, Grisdale & Van Alen

C. S. & D and LW, C & W - Cochran, Stephenson & Donkervoet and Lucius White, Clay & White

J. E., C&K - Justement, Elam, Callmer & Kidd

TABLE II - NEW CONSTRUCTION 1963

Building	A/E	Plans Completed	Contract Awarded	Contractor	Amount In Thousands	Completion Date*	Construction Schedule (Months)	Contract Overrun (Months)**
Surgical Wing (10-A) Instr.	NIH-IEDB	3/1/62	6/26/62[1/+]	Sanborn Co.	300	4/30/63[2/]	10	3
Power Plant (11-C)	Nottingham Associates	9/9/60	11/28/60	W. G. Cornell Co.	1,125	11/28/61[3/]	12	8
Cage Washing (14-F-1)	PBS	4/1/61	7/4/61	Victor Beauchamp	523	8/27/62[4/]	13	0
National Library of Medicine (38) MEDLARS	O'Connor & Kilham	10/29/62	12/17/62	J. Grimberg	60.3	6/5/63	6	0
NLM (38) Road & Sidewalks	PBS	9/17/62	10/30/62	F. O. Day	187.4	1/14/63	2.5	5
NIH Animal Center Ph. I	Hayes, Seay, Mattern & Mattern	3/13/63	6/21/63[5/]	J. McShain, Inc.	3,103	11/11/64[6/]	17	—

* By terms of the contract.

** Delay beyond the completion date.

\+ See following page for footnotes.

TABLE II - NEW CONSTRUCTION 1963 (Footnotes)

1/ Delayed as a result of contract negotiations.

2/ Operational use of all instrumentation systems was accomplished during midsummer 1963; however, correction of deficiencies and omissions continued throughout the calendar year.

3/ Operational use of the major systems was accomplished during the summer of 1962; however, several significant deficiencies and omissions were not completed until spring 1964.

4/ Operational use of the facility was accomplished during the summer of 1962; however, corrections of several minor deficiencies and omissions were not completed until late 1963.

5/ Delayed due to high bidding and insufficient funds.

6/ Construction is estimated to be 60% complete as of 7/1/64.

June 1964

January 1, 1963 through
June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-8
Serial Number

2. INSTRUMENT ENGINEERING AND DEVELOPMENT BRANCH
Branch

3. Dr. Fred Alt
Branch Chief

I. SUMMARY

The Instrument Engineering and Development Branch renders support to medical research and patient care at NIH in all areas of biomedical engineering. This includes engineering methods of medical investigations, development of new instruments and materials used for diagnosis, surgery, or treatment of human patients or research animals, and materials for artificial internal organs or implants. It also includes methods and instruments for the acquiring, transmitting, recording, and measuring of laboratory research data and of animal and patient physiological data during surgery, treatment, or recovery.

II. BRANCH PROGRAMS

A. Objectives

To render engineering and technical support to the intramural scientists and surgeons at NIH through consultation and advice on engineering methods and instrumentation systems applicable to clinical and laboratory medical research, and through design, construction, and maintenance of nonstandard scientific instruments.

To stimulate interest among scientists, engineers, and students by presenting a clear picture of the biomedical engineering field, its importance to medical progress, its career opportunities, and its educational requirements.

To cooperate with biomedical engineering activities outside NIH by disseminating information on new developments, supplying engineering and technical knowledge, and suggesting organizational patterns for biomedical engineering support facilities as requested.

B. Current Programs

In broad perspective, the Branch has three basic programs designed to achieve the Branch objectives: (1) biomedical engineering support in several engineering and life science disciplines; (2) fabrication of prototype specialty instruments not available commercially, and alteration or modification of commercial equipment as necessary to meet the needs of biomedical research, and (3) maintenance failure diagnosis and repair of biomedical instruments and instrumentation systems.

Specific activities support the NIH research programs and further biomedical engineering knowledge and applications in this country and abroad. The Branch is organizationally designed for flexibility to adjust its support methods to particular needs (for instance, full-time or part-time teamwork within a research laboratory, independent consultation service remote from the laboratory, engineering liaison between investigator and outside contractor, and cooperation with engineers and technicians of individual laboratory staffs), to expand its subject matter to cover the many specialty fields, and to acquire additional knowledge in new fields as they develop; i.e., biomedical telemetry, biomagnetism, physical models and simulation in life science research, etc.

In addition to rendering intramural engineering support, the staff provides a biomedical engineering review of patent reports by NIH staff members and grantees. When such review is requested of this Branch, one or more engineers experienced or knowledgeable in the specialty area involved review the report and render an opinion as to the novelty and utility of the discovery, as well as identifying printed publications or prior use or sale of similar inventions. Further, recommendations are made for or against patenting, depending on whether control of the invention is advisable for health or safety reasons; whether it is of potential significance to the public health, safety and welfare; and whether assurance against rival claims is desirable.

As the increasing complexity of modern medical research instruments and instrumentation systems requires ever greater engineering knowledge and experience for their operation, for failure diagnosis, and for programmed preventive maintenance, attention is directed toward providing satisfactory, high quality service in this area. This program acquires particular urgency

during surgical operations or critical experiments when equipment failure could have dire consequences.

The Branch uses various means to help promote the awareness of biomedical engineering potentialities among future and present engineers and scientists, such as publishing articles in professional journals on the biomedical engineering activities at NIH; addressing educational meetings; advising on fellowship awards to biomedical engineering students; holding personal discussion with university staffs on educational requirements and with department heads, placement officers, and students on the humane importance of the field and its career opportunities; and participating in the efforts of the Office of Education, DHEW, to arrive at a national curriculum guide for training in instrumentation technology.

As a pioneer in biomedical engineering and because of the cumulative years of professional experience of the staff, the Branch is frequently asked to assist outside organizations by supplying technical knowledge or suggesting methods of organizing biomedical engineering support facilities. Media through which this information is provided are articles in professional journals, patent reports, and personal conferences. Previously published or patented engineering developments are made available upon request to universities and research organizations outside NIH or to commercial manufacturers.

Branch members actively participate in biomedical engineering committees of national professional societies and the Engineers Joint Council.

C. Program Progress and Accomplishments

1. Engineering Advances

Items of major advances in engineering methods, development, design, and fabrication of instrumentation as applied to medical research and considered biomedically significant to the NIH program were:

Blood Flow Valve This fast acting valve, when actuated by one heart beat, will shunt the arterial flow into a pneumatic impedance for the next beat and then return the flow to its normal channel for the third beat. The device allows a study to be made

of the rate at which the heart reacts to changing stress conditions on a beat-by-beat basis.

Cardiac Force Gage A force gage used for measuring the changes in frequency and force of contraction of heart muscle in vivo. It consists of a strain gage bridge mounted on flexure plates and affixed to a frame containing probes which can be inserted into the muscle. Two different models of the device are now in use.

Cardiac Pacemaker The useful life of implanted cardiac pacemakers has been limited by the flex-fatigue of the leads which carry the electrical impulse from the implanted oscillator. The Branch evaluated the relative life of four different lead configurations commercially available and a promising steel alloy, Eligiloy. A machine was designed and fabricated which would flex samples at rates up to 2000 times per minute (approximately 30 times normal heart rate). Results of tests indicated that resistance to flex-fatigue varied for the different metals and configurations. Specially processed Elgiloy leads produced under the direction of the Branch showed best flex-fatigue resistance.

Head Accelerometer Instrumentation A special means of mounting two miniature accelerometers on a monkey's skull permits recording of acceleration during a controlled impact. The data, as well as additional EEG and EKG data, are filtered, amplified, presented on an oscilloscope display, and recorded photographically. This permits correlation between conditions during impact and the resulting concussion.

Muscle Force Gage This special mounting system permits a patient to be placed in a variety of positions in order to measure the strength of each set of extensor and retracting muscles associated with each joint of the arms or legs of the patient.

Tooth Incubator An apparatus which permits an accelerated study to be made of factors affecting the decay of teeth. Test teeth are placed in an incubation chamber and a variety of test fluids and washes can then be programmed into the chamber. The exposure time for each fluid can be selected over a wide latitude, and the recycling time of any particular study is limited only by the size of the reservoirs.

Tooth Mobilometer A device used to measure and record the amount of wobble or mobility of an individual tooth. It is intended as an aid in the study of jaw and gum diseases. The

device can apply a known force either to push or pull on a tooth and measure its displacement as a function of time.

2. Contractual Support

As the requests for services from the Branch for engineering, fabrication and maintenance continue in increasing measure, the utilization of contracts with outside firms increases commensurately. In keeping with this program, the Branch engineers and supervisors have become thoroughly acquainted with the capabilities of outside firms, with handling and monitoring of outside contracts for engineering and development, and with the design, fabrication and maintenance of instrumentation. The Branch recently organized a filing and cross-indexing system for information on consultant firms and manufacturers active in biomedical engineering for ready retrieval of commercial support capability.

3. Preventive Maintenance and Technical Assistance

The experimental and clinical nature, together with the continued growth, of intramural research at NIH has created an increasing demand for preventive maintenance, timely on-site diagnosis and repair, and operations work on the biomedical instrumentation systems. The need for such service covers not only new and complex instrumentation developed and fabricated by the Branch, but also large and costly commercial instrumentation. To meet this need, a new section was activated at the beginning of Fiscal Year 1964 and was staffed with personnel possessing special training to provide the high level skills and abilities needed to perform this work.

4. Area Shops

The facilities and capabilities of the Building 10 satellite shop were expanded by the addition of new personnel, including a glassblower. This unit, although still understaffed, can offer Clinical Center researchers and investigators quicker service on routine and emergency jobs by eliminating the time lag previously required when sending instruments to or requesting service from the parent facility located in Building 13.

D. Problems

Inadequate space and insufficient personnel to meet the increasing work load continue to be the major obstacles impeding the progress and growth of the Branch, thus limiting its service to NIH.

Plans now call for the addition of approximately 7000 sq. ft. within the next year, and an additional 3000 sq. ft. soon thereafter. This should considerably relieve the space problem.

The imposition of personnel ceilings on the number of people employed in sections financed by the Service and Supply (Revolving) Fund greatly reduces the effectiveness of performing services requested by NIH users of the Branch facilities. This has been met to some degree by use of outside contractors. Commercial resources are insufficient, however, to meet the total backlog; consequently, overtime work by regular employees is used with limited success to combat the problem.

E. Program Plans

In its effort to give optimum service to NIH in this very new and rapidly changing field of biomedical engineering, the Branch constantly has to adjust its program to new conditions. One of the major developments expected for the near future is that of increasing interest and participation of commercial consultants and manufacturers in medical instrumentation. This will provide a growing supply of available engineering and instrumentation support. NIH can expect to gain increasing benefits from this situation. The program plans of this Branch are directed toward tapping these commercial resource facilities and making them available to NIH scientists and surgeons. This is not a new program; the Branch has, in the past, established and monitored outside contracts in support of NIH projects. The expansion in commercial availability, however, requires planning for an increase and strengthening of this Branch program. The recently organized information gathering and filing system mentioned in an earlier part of this report (paragraph II.C.2) is a first step in this direction.

F. Publications, Patents and Presentations

1. Publications

Books

Alt, F. (Ed.): Biomedical Sciences Instrumentation, Vol. I. Proceedings of the First National Biomedical Sciences Instrumentation Symposium. New York, Plenum Press, 1963, 475 pp.

_____: Supply and demand in biomedical engineering: an introductory address. In Alt, F. (Ed.): Biomedical Sciences Instrumentation, Vol. I. Proceedings of the First National Biomedical Sciences Instrumentation Symposium. New York, Plenum Press, 1963, pp. 1-3.

Cohen, G. S. and Morrow, A. G.: An instrumentation system for cardiovascular surgery. In Proceedings of the 1963 16th Annual Conference on Engineering in Medicine and Biology, Baltimore, Maryland, November 18-20, 1963. Baltimore, The Conference Committee for The 16th Annual Conference on Engineering in Medicine and Biology, 1963, Vol. 5, pp. 52-53.

Pearlman, W. and Baldwin, M.: Experimental designs in the study of biological effects during radio frequency transmission. In Alt, F. (Ed.): Biomedical Sciences Instrumentation, Vol. I. Proceedings of the First National Biomedical Sciences Instrumentation Symposium. New York, Plenum Press, 1963, pp. 157-166.

Journal Articles

Alt, F.: Today's new team/the M.D. and the P.E. American Engineer 33(8): 29-33, Aug. 1963.

_____: Instrumentation for biomedical sciences. Science 142: 249-252, Oct. 11, 1963.

_____: Organizational patterns of engineering support for biomedical research. Amer. J. Med. Electronics 2: 316-321, Oct.-Dec. 1963.

Byck, R. and Dirlik, P.: Reversible section of the brain by a wall of cold. Science 139: 1216-1218, Mar. 22, 1963.

Carmeci, P. and Jorgensen, R.: Sonograph recording techniques. Journal of the Acoustical Society of America. In press, 1964.

Crisp, L. R.: A new pipette washing machine. Lab. Pract. 13: 43-45, Jan. 1964.

Dirlik, P. and Posner, H.S.: Automatic spraying of paper chromatograms: an apparatus based on rotary motion suitable for quantitative analysis. J. Chromatogr. 10: 250-252, Feb.1963.

Elmore, S. M., Sokoloff, L., Norris, G., and Carmeci, P.: Nature of "imperfect" elasticity of articular cartilage. J. Appl. Physiol. 18: 393-396, Mar. 1963.

Friauf, W. S.: Dynamic characteristics of analog to digital converters. Instruments and Control Systems. In press, 1964.

Hansen, C. A., Nolan, J. P., Jr., Freeman, M. E., Dow, J. W., and Alt, F.: Biomedical engineering resources: problems in a cross-disciplinary science. Med. Electronics & Biol. Eng. 1: 401-406, Aug. 1963.

Riggle, G, C. and Rector, D. A.: A portable densitometer for establishing cleaning standards. Journal of Environmental Health 26(4): 250-251, Jan.-Feb. 1964.

Riggle, G. C. and Weisburger, J. H.: Gas bubble and liquid flow detector, an automatic control system for column chromatography. Anal. Chem. 36: 1167-1168, May 1964.

Simon, G. A. and Alt, F.: Biomechanical engineering. Mech. Eng. 86(5): 32-35, May 1964.

Vurek, G. G. and Conlon, J. M.: Electromechanical shutter for ultraviolet time-lapse photomicrography. Rev. Sci. Instr. 34: 583-584, May 1963.

2. Patent Suggestions

January 1964--Microtome Section Pickup and Manipulator
Howard D. Metz

March 1964 --A New Pipette Washing Machine, Laurence R. Crisp

April 1964 --Portable Densitometer with Integral Power Supply
Grant C. Riggle and David A. Rector

3. Presentations

Riggle, G. C.: Development of heart-lung bypass system. Fifteenth Annual Symposium on Flow Measurement Principles and Problems sponsored by the Instrument Society of America. April 1963.

Alt, F., Cohen, G. S., and Simon, G. A.: Medical engineering. Panel discussion presented to the Naval Reserve Research Company, 5th Naval District. September 1963.

Cohen, G. S.: Engineering aspects and significance of the instrumentation system in the new operating rooms. Dedication ceremonies of the New Surgical Wing (Building 10A), NIH. September 1963.

Alt, F. and Simon, G. A.: Biomedical engineering at the National Institutes of Health. Annual Meeting of the American Society of Mechanical Engineers. October 1963.

Heitlinger, L. J.: Engineering considerations for standardizing the scoring of electrical skin phenomena data. Annual Meeting of the Society of Psychophysiological Research. October 1963.

Alt, F., Cohen, G. S., and Simon, G. A.: Progress in medical engineering. Panel discussion presented to the Frederick Chapter of Maryland Society of Professional Engineers, the Chemical Engineers Club of Central Maryland, and the Western Maryland Section of the American Society of Mechanical Engineers. January 1964.

Bradfute, G. A., Jr. and Simon, G. A.: Engineering contributions to medical progress. Baltimore Section of the Instrument Society of America. February 1964.

Alt, F.: The status of biomedical engineering and instrumentation in the United States. Seminar at the U. S. Trade Center in London, England, in connection with the U. S. Department of Commerce Exhibition of "Electronics for Medical Diagnosis and Monitoring." April 1964.

Riggle, G. C.: Instrumentation developments for biomedical research program, National Institutes of Health. Virginia Mountain Section of Institute of Electrical and Electronic Engineers. May 1964.

Simon, G. A.: Special instruments for surgery and bio-medical research. Spring meeting of the American Surgical Trade Association. May 1964.

Serial No. 8.1
1. Instrument Engineering and Development Branch
2. Electronic Engineering Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Conversion of Gradient Elution Control System to Punched Tape

Principal Investigators: Charles J. Ramsden, Grant C. Riggle

Other Investigators: Dr. David F. Johnson

Cooperating Unit: National Institute of Arthritis and Metabolic Diseases, Laboratory of Chemistry

Man Years (January 1, 1963 through June 30, 1964)

Total:	0.3
Professional:	0.1
Other:	0.2

Project Description:

Objective. To provide an infinitely variable means of controlling the mixture ratio of two eluants introduced in column chromatography, permitting the polarity of the eluting solvent mixture to be increased or decreased as desirable.

Methods Employed. A punched tape programmer was developed which permits as little as an 0.2 percent change in the ratio of two eluants whose total volume is a constant. Through the new design, extreme changes in the desired ratio can be accomplished in adjacent sequence, and with a repeatable accuracy limited only by the selected electronic components.

Significance to Biomedical Research. The development permits the selective and controlled separations of adrenocortical hormones through precise control of eluting solvent mixture polarity. Although the initial studies were directed toward adrenocortical hormones, other important uses are currently under investigation because of design adaptability. The versatility of the apparatus has been expanded further to meet the special interest in radioactive tracer methods for determining metabolites or transformation products.

Part B Included Yes

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Francois, D., Johnson, D. F., and Heftmann, E.: Programmed gradient elution chromatography with the steroid analyzer. Anal. Chem. 35: 2019-2022, Dec. 1963.

Serial No. 8.2

1. Instrument Engineering and Development Branch
2. Engineering Development Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Instrumentation System for Cardiac Surgery

Principal Investigators: Gerald S. Cohen
Dr. Andrew G. Morrow

Cooperating Unit: National Heart Institute
Cardiac Surgery Branch

Man Years (January 1, 1963 through June 30, 1964)

Total:	0.3
Professional:	0.3
Other:	.0

Project Description:

Objective. To provide the cardiac surgeon and the operating staff with an instrumentation system for monitoring and displaying critical physiological parameters and recording significant data generated during the operative procedure.

Methods Employed. The system can handle the following inputs: 5 pressures, 5 temperatures, 2 electrocardiograms, 2 electroencephalograms, 1 pulse plethysmograph, 1 dye dilution, 1 blood flow, 1 blood loss. Two of the pressure channels are electronically processed to extract systolic, diastolic and mean values. Heart rate is derived from EKG, pressure, or pulse plethysmograph wave. The dye dilution curve is processed in a special computer to yield an instantaneous measure of cardiac output. A unique display technique presents systolic, diastolic, and venous pressure, temperature, heart rate, blood flow and blood loss in the

operating room in numerical form. An eight-channel magnetic tape records the dynamic data. This information is also displayed on a large screen oscilloscope and a photo oscillograph. Numerical information is plotted on a multipoint recorder.

Significance to Biomedical Research. The assembly of this integrated system of amplifying, processing and recording devices provides a unique opportunity to carry on complex physiological studies of great importance. The convenience of having this equipment available in the operating room at all times makes it unnecessary to assemble and integrate large amounts of equipment for every special study that is made. Studies have been made to examine the relationships amongst blood flow, pressure in the various chambers of the heart, and the contractive force of the heart. The numerical display of vital data in the operating room assists in the clinical management of the patient and eliminates much voice communication traffic.

Part B Included Yes

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Cohen, G. S. and Morrow, A. G.: An instrumentation system for cardiovascular surgery. In Proceedings of the 1963 16th Annual Conference on Engineering in Medicine and Biology, Baltimore, Maryland, November 18-20, 1963. Baltimore, The Conference Committee for The 16th Annual Conference on Engineering in Medicine and Biology, 1963, Vol. 5, pp. 52-53.

Serial No. 8.3

1. Instrument Engineering and Development Branch
2. Engineering Development Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Patient Monitor for Cardiac Recovery Room

Principal Investigators: Gerald S. Cohen
Dr. Andrew G. Morrow

Cooperating Unit: National Heart Institute, Surgery Branch

Man Years (January 1, 1963 through June 30, 1964)

Total:	0.2
Professional:	0.2
Other:	.0

Project Description:

Objective. To provide instrumentation that will assist the attending physician and the recovery room staff in the clinical management of the postoperative cardiac patient.

Methods Employed. The system monitors electrocardiogram, arterial pressure, venous pressure and temperature. The information is further processed to obtain systolic, diastolic or mean pressure and the heart rate. The processed data is presented on large meters, while the original data is displayed on a four-channel oscillograph. A single channel hot stylus recorder allows a permanent record to be made of any one of the channels. Provision is made for connection of a multichannel tape or graphic recorder. An alarm system indicates abnormal conditions such as tachycardia or bradycardia, and cardiac arrest is incorporated in the system. An internal-external pacemaker with automatic control is part of the device.

Significance to Biomedical Research. The mobile, easy-to-operate monitor represents a significant improvement in patient care. It relieves the recovery room personnel of much routine testing of the patient and allows them to tend to his other needs. The signal processing equipment preserves the fidelity of much of the original dynamic information which can be utilized in various investigative programs by attaching the appropriate recording devices.

Part B Included No

Serial No. 8.4

1. Instrument Engineering and Development Branch
2. Mechanical Engineering Section
   Electronic Engineering Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Nucleic Acid Analyzer

Principal Investigators: Frank O. Anderson, David A. Rector, Grant C. Riggle

Cooperating Unit: National Institute of Mental Health
Laboratory of Cellular Pharmacology

Man Years (January 1, 1963 through June 30, 1964)

Total:	0.6
Professional:	0.2
Other:	0.4

Project Description:

Objective. To automate a number of laboratory procedures used to detect the presence and quantity of nucleotides, peptides and proteins, and automatically record the derived information.

Methods Employed. The nucleic acid analyzer is an automated instrument used to detect and record the presence of nucleotides in the effluent from prepared chromatographic columns. A commercial monochromator is used in association with an IEDB designed flow cell system. Variance in absorption at selected wavelengths of the solution is detected by a photoelectric circuit and the signal integrated to record directly in absorption values. Associated programming controls permit a variety of eluants to be introduced into the column. The apparatus is entirely automatic after initial preparation and may be operated for weeks unattended.

Significance to Biomedical Research. The apparatus provides the laboratory with an instrument for making biochemical determinations on an automated and unattended basis, thus releasing laboratory personnel for other assignments. In addition, it provides the research scientist with a continuous record of qualitative and quantitative values of nucleotides extracted from yeast.

Part B Included No

Serial No. 8.5

1. Instrument Engineering and Development Branch
2. Engineering Development Section
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
January 1, 1963 through June 30, 1964

Part A

Project Title: Microelectrode Preamplifier

Principal Investigator: Walter S. Friauf

Cooperating Unit: National Institute of Neurological Diseases and Blindness
Surgical Neurology Branch

Man Years (January 1, 1963 through June 30, 1964)

Total:	0.2
Professional:	0.2
Other:	Negligible

Project Description:

Objective. To provide a preamplifier suitable for amplifying neuron action potentials from the human brain in an operating room setting.

Methods Employed. A miniature amplifier utilizing a field effect transistor in a package one-half inch in diameter and one inch long, weighing approximately 15 grams, was designed and fabricated. The 1000 megohm input impedance and a band pass of 15 cycles to 100 kilocycles of this device meet the requirements for recording from metal microelectrodes. The unit can be repeatedly gas sterilized without deleterious effects.

Significance to Biomedical Research. This device fills a need in neurological operating room research equipment not previously met. Its size, weight and performance characteristics make it possible to carry on the research program in microelectrode recording from the human brain. Previous equipment used in the laboratory for this type of work was bulky and unwieldly and could not be sterilized. The development of this amplifier was therefore essential to moving microelectrode recording work from the laboratory to the operating room.

Part B Included No

June 1964 January 1, 1963, through June 30, 1964

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

Summary of Branch Activities

1. DRS-9
Serial Number

2. Library Branch
Branch

3. Jess A. Martin
Branch Chief

I. SUMMARY

The 18 months covered by this report represent a period of invaluable and significant consequence to the NIH Library and to the support it provides the research program of the National Institutes of Health. All operations within the Library have been subjected to close scrutiny. Projects designed to improve all library services as quickly as possible have been introduced.

Reorganization of the service program of the Library was begun on February 1, 1963, when a new Chief, Library Branch was appointed. Administratively, the Library was reorganized to include the Office of the Chief, and Readers Services, Technical Services, and Bibliographical Services Sections. Recruiting was begun immediately for qualified persons to assume responsibilities as Section Chiefs and has resulted in appointment of two of the three Section Chiefs required by the new staffing plan.

Reorganization of the Library staff as a cohesive, responsive, stable service body was given immediate attention. Acting Heads of Units were provided permanent titles. Part-time employees were encouraged to assume full-time duties. Whereas 12 part-time employees occupied full-time personnel slots in 1963, only 2 remained on the Library staff in 1964, and even they had increased their hours from 6 to 7 per day. This better manpower utilization resulted in improved service being provided those participating in research at NIH.

Recognizing their responsibility to serve the NIH staff more effectively, professional librarians agreed to alternate working evenings and weekends. At the time of this report the NIH Library is manned 138 hours of a possible 168 hours per week.

Attention was also directed to the collection and to the physical facility. Order was brought to the journal collection as a result of a complete inventory, and a want list of missing issues was begun. Both journal and monographic collections were weeded to provide space for new volumes and remove little-used obsolete material. Two crash programs resulted in binding 10,000 volumes in addition to the number normally bound during a year. It appears that book losses were curtailed after physical changes were made which permitted closer supervision of the collection.

Not least important during the period covered by this report was the presentation of the program of requirements for relocation of the NIH Library to new quarters.

Included in the reorganization of the Library was the reactivation of the Library Advisory Committee. Members, representing nearly every Institute and Division, assist with the identification and interpretation of the needs of the research scientists who use the facilities and services of the Library. Anticipated assistance of the Library Advisory Committee will allow the Library staff to become better acquainted with the literature needs of the NIH scientists and will encourage further improvements in the service program of the Library.

II. BRANCH PROGRAMS

A. Objectives

The primary mission of the Library Branch is to operate an efficient comprehensive library to support the research programs and administration of the NIH Institutes and Divisions. Its activities include the acquisition, maintenance and circulation of library materials; the operation of a photocopying service; the provision of information, reference and bibliographic assistance; and the provision of a translating service for foreign scientific literature. To fulfill its mission effectively the Library must be responsive to the changing literature needs of the NIH investigator and knowledgeable of current technological methods applicable to scientific library services.

B. Current Programs

Readers Services

Readers services to the NIH staff include reference and bibliographic assistance, circulation of literature, photocopying service, and translating service.

The Reference staff compiles short bibliographies on specialized subjects and performs comprehensive literature searching as requested by NIH investigators. In order to answer the multitude of inquiries for specific information, the reference librarians endeavor to keep abreast of the activities of NIH and other research institutions and of biomedical developments through attendance at lectures, personal reading, and course instruction. In this way they are also strong contributors to the book and journal selections program. As much personal contact with the scientist-user as possible is maintained in order to appreciate better his specific needs.

The Circulation Unit, through constant surveillance of the collection and its use, maintains the materials in such a manner as to encourage greater and easier access for the patron. Extensive use of the photocopy service within the Circulation Unit allows greater and more frequent use of circulating library literature. A considerable activity of this Unit is the inter-

library loan program which increases the availability of books and journals required by NIH scientists.

Another vital service offered by the Readers Services Section is the translation of foreign language articles into English. Most of the European languages are handled by several of the staff translators. Other languages are translated by contractors, with the NIH Library handling the arrangements.

Technical Services

Technical services include the acquisition of books, journals, and other printed materials needed to support the research efforts of NIH scientists and the processing of these materials for use. Processing includes classification, subject and descriptive cataloging, and preparation of the books for use. Constant review and revision of the card catalog is necessitated by the changing needs of the scientist-users. A gift and exchange program permits valuable materials to be added to the collection at little cost to the Library. An extensive binding program improves the availability and useability of the collection.

Bibliographical Services

Although the concept of bibliographical support for the scientist through close liaison with the programs of the Institutes was approved in June 1963, this program has only recently been initiated, and on a limited scale.

C. Program Progress and Accomplishments

Readers Services

1. Photocopying Service. A microfilm system was introduced in 1963 to provide more efficient service and to increase the Library's capability for providing photocopies. Two Xerox 914 Photocopiers were retained for urgent requests of 12 pages or less. On the recommendation of the Library Advisory Committee and the Scientific Directors, a pilot study of the use of coupons for photocopy service was instituted with the dual objective of identifying the users of the photocopy service and of determining whether this coupon system would ensure a more effective use of this vitally important service.

2. Interlibrary Loan. During 1963, 9,000 volumes needed by NIH investigators were borrowed from area libraries, and 5,000 volumes were loaned to other libraries. In 1962, 12,000 volumes were borrowed and 2,000 volumes loaned. The decrease of 3,000 volumes borrowed from other libraries in 1963 may reflect the improved condition of the Library's collection, made possible by increased budgetary support for books and journals, the security measures adopted, and improved stacks maintenance techniques.

3. Orientation. During 1963, general explanations and tours of the Library were given to 210 patrons in groups of from 3 to 20 persons. More intensive orientations relating to methods of literature searching,

special reference indexes, journals and monographs, and specific information problems were given to 350 investigators. Orientation activities for 1964 are following the same pattern. The NIH Library Guide which describes the services of the Library is now available.

4. Reference Service. Several well-qualified reference librarians with scientific and/or medical background have been added to the staff to fill vacancies. Emphasis has been placed on supplying immediate information to the investigator over the phone or in person. The activities of the reference librarian include scanning current journals, publishers' catalogs, and announcements for current in-scope publications and evaluating them for acquisition by the Library.

Ninety-three bibliographies were prepared by the Reference Unit on subjects requested by NIH investigators. In addition, certain bibliographies were prepared on cards and numerous bibliographies are in process. One bibliography, entitled Cancer in Sub-Human Primates, is being issued as part of the Public Health Service Bibliography Series.

5. Circulation - Overdue Journals. A systematic effort was made early in 1964 to eliminate the backlog of overdues. Some 3,500 notices were mailed or phoned to patrons charged with overdue journals. In response, many journals which had been held weeks and months in laboratories and offices were returned and became available for use on the library shelves. Similar attention will soon be given to the backlog of overdue books.

6. Translating. As a result of a management study, certain changes were instituted to increase the effectiveness of the translation service. Production standards were established for all translator grades. New procedures required that the Library's budgetary allotments be made annually to each Institute or Division for free contract translating service. When allocated funds have been exhausted, the Institute or Division bears the cost of additional translating service. Assignment of additional space to the Translating Unit provides better accommodations, with partitioned offices affording a degree of privacy to each translator and sufficient space for oral translating. Until the better accommodations were provided, oral translations were handled in a noisy corridor outside the offices of the translators.

Technical Services.

1. Acquisitions. Effective April 1, 1963, the Library Branch gained approval to adopt the blanket order method of acquisitions. Under this plan, in-scope books are received on approval from reputable publishers of medical and scientific books and from certain dealers. This system of ordering books lessens delay and eliminates much paper work. Searching and typing orders are now performed directly from source materials used by selectors of new acquisitions. Consolidation of numerous separate files has eliminated duplication of effort and has resulted in a considerable savings in staff time.

During this 18-month reporting period, the Library's collection was

strengthened by the purchase of approximately 5,700 new books and by the receipt of 570 books through gift or exchange. For 1964 the Library has subscriptions to more than 2,000 journal titles, with an additional 800 received through gift or exchange, representing an increase of 220 over 1963.

Considerable work is in progress to bring the serial record up-to-date using the information of missing volumes and issues obtained from the inventory of the journal collection. These records are also being consolidated into one record for greater efficiency.

Special attention was given to the binding of completed journal volumes through a crash program of assembling and preparing the issues for the bindery. During this 18-month period more than 15,000 volumes were bound.

2. Cataloging. Under new leadership, steps were taken to analyze procedures and methods in order to simplify routines and improve the efficiency of processing new publications. The Serial Locator has been completely revised.

3. Satellite Libraries. Additional support to NIH programs was given through satellite libraries which the Library Branch established and helped maintain. There were three satellite libraries at the start of 1963, but one, in the Research Facilities Planning Branch, was later transferred back to the NIH Library. Operations and services remained unchanged for the other two satellite libraries.

4. Publicity. During the 18 months covered by this report, in order to acquaint NIH personnel further with the services provided, 16 articles and announcements related to the activities of the Library appeared in the NIH Record. Among the more important articles were an historical account of 60 years of Library service, an illustrated description of the new Xerox Copyflo system, and several announcements concerning Library exhibits. The exhibits, prepared by various members of the Library staff, have attracted considerable attention and favorable comment. Assistance with the exhibits was provided by the Medical Arts and Photography Branch. On display were recent publications authored by NIH personnel, basic current publications on instrumentation, all 11 editions of the Children's Bureau publication Infant Care, 1914-1963, and punched card systems for information retrieval.

D. Problems

The greatest problems faced by the NIH Library result from turnover of personnel, lack of personnel to develop proposed new programs, and the need for space. During the period covered by this annual report, 25 of the clerical and subprofessional staff and 8 of the professional staff left the employ of the NIH Library. Part of this turnover was invited by the Librarian, who encouraged the 12 part-time employees to work full-time or find other employment. Reasons given for resigning would suggest that a general upgrading of the clerical and stacks maintenance positions, with higher beginning grades, would help resolve the problem by attracting better qualified employees.

Personnel turnover is not unique at the NIH Library. Many libraries across the country encounter rapid turnover of clerical personnel. Admittedly, upgrading positions would only partially solve the problem but would at least represent a step in the right direction.

During the period covered by this report, the Library has greatly improved its service functions, but lack of personnel has not allowed much progress to be made with new programs such as bibliographical services and automation of library functions.

The proposed new library building will solve several problems related to the need for additional space and space of a different configuration than is now occupied. Presently, adequate space is not available for staff, book storage, and reading or study areas. The present library space is difficult to supervise. It appears, however, that the security measures adopted in March 1963 have helped to reduce book losses. In the new library building the security problem will be reduced by having only one exit which will be supervised.

The new building will allow serious consideration to be given to the integration of several special collections within the NIH Library which present administrative problems and patron inconveniences.

In the meantime weeding of the collection will represent the best approach that can be taken to combat congestion on the shelves.

E. Program Plans

Partial implementation of the Bibliographical Services Section is planned to improve the effectiveness of the service program of the NIH Library. Liaison with the Institutes and Divisions will provide better understanding of their literature and information needs. Service of this type is being requested and the library program should respond to the request.

Consideration will be given to additional physical changes that conceivably could reduce the number of inconveniences now being encountered by the patrons. Weaknesses in the present security system will be studied to determine how they can be eliminated.

In anticipation of continuing staff turnover, an Internship Program for librarians is planned. The program will attract well-qualified Library School graduates, who will receive training in all areas of librarianship and who will be eligible for jobs in the NIH Library upon completion of their 40-week training session.

In order to reduce the costs of the photocopy service, a recommendation that the Xerox Copyflo be purchased instead of leased has been made. Purchase would result in an estimated annual savings of $6,000.

Feasibility studies will be conducted to determine whether certain functions of the Library can or should be automated. Functions to be studied initially are serial recording, book ordering, and circulation.

F. Publications

The NIH Library Guide, an illustrated brochure which describes the services of the Library, was distributed early in 1964.

Periodicals Currently Received in the NIH Library which was compiled, printed, and distributed in 1964 represents a complete revision of the 1961 edition.

Index of Translations, 1954-1963 indexes by author the Library's collection of 5,000 translations.

Recent Translations - A Selected List presents a monthly listing of selected articles currently translated by the Translating Unit of the Library.

NIH Booklist appears bimonthly as a bibliographical record of major book and journal accessions in the Library.

Cancer in Sub-Human Primates, a bibliography compiled by Marjorie Luther, a former Reference Librarian, is being published as a part of the PHS Bibliography Series.

"Photocopying in a Researching Library," by Jess A. Martin and Malcolm S. Ferguson, appeared in the April 1964 issue of the Bulletin of the Medical Library Association, pages 410-413.

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